Tetrahedron 67 (2011) 5054–5068

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formal total synthesis of the myxobacteria metabolite apicularen A via a transannular oxy-Michael addition

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ARTICLE INFO

Article history:
Received 18 February 2011
Received in revised form 17 March 2011
Accepted 5 April 2011
Available online 11 April 2011

ABSTRACT

The formal total synthesis of the myxobacteria metabolite (−)-apicularen A (**1**) is described. The key step utilized to construct the 2,6-*trans*-disubstituted tetrahydropyran ring was the transannular oxy-Michael addition of enone (+)-**48** to form *trans*-pyranone (+)-**50**. Cyclisation of the C13 epimer (−)-**49** also gave the same *trans*-pyranone (+)-**50** demonstrating that the stereochemistry of the apicualren ring system can be controlled only by the C15 asymmetric centre. Reduction of the ketone in (+)-**50** and demethylation gave the advanced apicularen intermediate **4** completing the formal total synthesis of the natural product **1**.

1. Introduction

Myxobacteria are Gram-negative, rod-shaped aerobic bacteria, which are common inhabitants of soil where they enjoy a rich social life.[1] These organisms have astonishing life cycles and upon starvation, undergo cellular morphogenesis converting to resistant myxospores, which are multicellular fruiting bodies that contain many thousands of cells, which have species-specific shapes.[2] Over the past two decades, myxobacteria have gained attention as an excellent source of bioactive compounds with novel structures.[3] Chemical investigation of several species of myxobacteria by Höfle and co-workers has resulted in the isolation of a number of interesting compounds, which possess both antibiotic and cytotoxic activity. The macrolides apicularen A (**1**) and B (**2**) (Fig. 1) were isolated in 1998 from a variety of strains of the myxobacteria genus *Chondromyces*, which include the species *Chondromyces apiculatus*, *Chondromyces robustus*, *Chondromyces pediculatus* and *Chondromyces lanuginosus*. *Chondromyces robustus* was used to produce apicularen A (**1**) and B (**2**) in larger quantities.[4,5]

Structural characteristics of these compounds are a 2,6-*trans*-tetrahydropyran, which is part of a 12-membered salicylate macrolactone and an unsaturated enamide side chain. Apicularen A (**1**) is remarkably similar to the marine sponge metabolite salicylihalamide A (**3**),[6] and it is not unreasonable to suggest that compound **3** may be a metabolite of a symbiotic marine myxobacterium species rather than the sponge itself. Indeed, it is also possible that tetrahydropyran ring in apicularen A (**1**) results from some type of a transannular cyclisation of a salicylihalamide type precursor. The

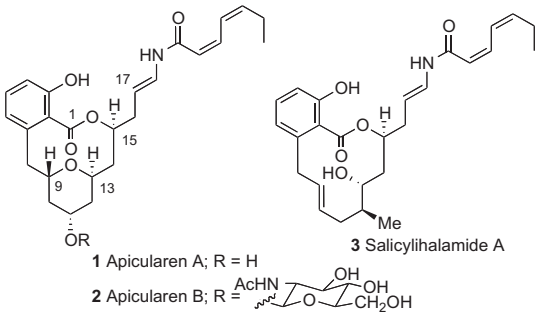

Fig. 1. Structures of apicularens A (**1**), B (**2**) and salicylihalamide A (**3**).

relative stereochemistry of **1** was confirmed by a single crystal X-ray structure whilst the absolute configuration was assigned by Mosher ester analysis.[4] Apicularen B (**2**) possesses the same macrolactone core and an *N*-acetyl-β-D-glucosamine residue at C11 as determined by extensive NMR analysis.

Isotope labelling experiments indicated that the biosynthesis of apicularen A (**1**) involves an acetate/methionine C3 starter unit with purely acetate-based elongation of the polyketide chain, which is only perturbed once by the incorporation of a glycine unit.[5]

Apicularen A (**1**) showed no antimicrobial activity but was found to be a powerful inhibitor of the growth of human cancer cells with IC_{50} values ranging between 0.3 and 3 ng/mL against several different human cancer lines. In addition, apicularen A (**1**) exhibits high potency against the multi-drug resistant cell line KB-V1.[3] This remarkable combination of effects suggests a novel mode of action. Apicularen B (**2**) was distinctly less cytotoxic but showed weak

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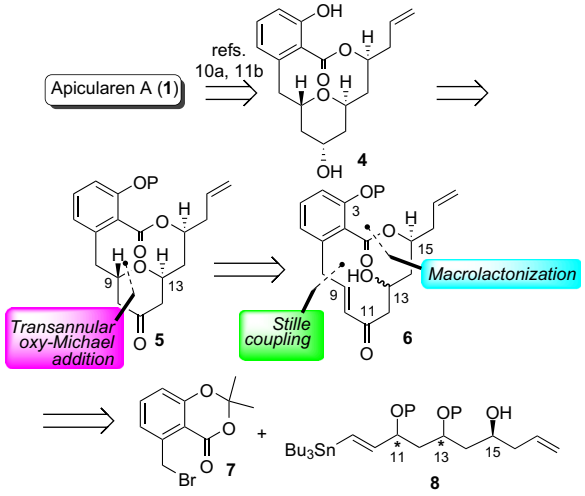
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.04.002

antimicrobial activity against a few Gram-positive bacteria, which include, *Micrococcus luteus* (MIC 12.5 μg/mL) and *Corynebacterium fascians* (MIC 25 μg/mL).[3] Apicularen A (**1**) also exhibits an extensive range of biological activities[7] and is a novel specific V-ATPase inhibitor[8] as well as a microtubule-targeting compound.[9]

The potent biological activity and novel structure of apicularen A (**1**) has attracted much attention from the synthetic community resulting in five total syntheses[10] and several formal total syntheses[11] as well as numerous synthetic studies.[12] In addition, a number of analogues of **1** have been synthesized and SAR studies on these indicated that the presence of a salicylate and enamide are important for biological activity while the macrocycle is not as critical.[10c,13] In this paper, we report the full details of our formal total synthesis of apicularen A (**1**), which utilizes a transannular oxy-Michael addition to form the 2,6-*trans*-THP ring with high stereocontrol.[11c,12d]

2. Results and discussion: retrosynthetic analysis

The retrosynthetic analysis of apicularen A (**1**) is shown in Scheme 1. Our target was the alkene **4**, which has been converted into **1**.[10a,11b] Compound **4** could easily be accessed from the ketone **5** by reduction and deprotection. Pyranone **5** would in turn be formed by a transannular oxy-Michael reaction of precursor enone **6**.



Scheme 1. Retrosynthetic analysis of apicularen A (**1**).

Thus, the salicylihalamide type intermediate **6** would be cyclised to the apicularen type *trans*-pyranone **4**. Several other approaches[10e,f,11d,e] have utilized a transannular etherification reaction to forge the 2,6-*trans*-THP ring of apicularen A however, the current approach is the only one which involves a transannular oxy-Michael reaction. The conjugate addition substrate **6** could be synthesized via a similar approach utilized in our reported formal total synthesis of salicylihalamide.[14] A Stille coupling between the bromide **7** and stannane **8** followed by a based induced macrolactonisation would afford the enone **6**.

We envisaged that the oxy-Michael addition of **I** to form pyranone **II** under thermodynamic control might favour formation of the apicularen 9,13-*trans*-13,15-*syn* relative stereochemistry (Fig. 2). Molecular modelling conducted on truncated pyranone isomers (MM2, AM1 and MMX force fields)[15] clearly showed a preference for the desired stereoisomer. Thus, if an equilibrium could be established, the stereochemistry at C9 and 13 could be equilibrated by a Michael/retro-Michael sequence leading eventually to 9,13-*trans*-13,15-*syn* diastereoisomer. In this way, the only relevant stereochemistry is the C15 asymmetric centre, which in the macrocyclic system controls the stereochemical outcome at the other centres. Thus, the configurations at C11 (oxidized to a ketone) and C13 (epimerizes) as marked on compound **8** (see Scheme 1) are not relevant. Interestingly, in all force fields, the twist boat (TB) conformer was preferred for the 9,13-*trans* isomers whilst the chair (C) conformation is preferred for the 9,13-*syn* isomers. The conformation of the THP ring in apicularen A is chair-like in the solid state (X-ray) but twist boat in solution as determined by NMR (NOE) analysis.[4]

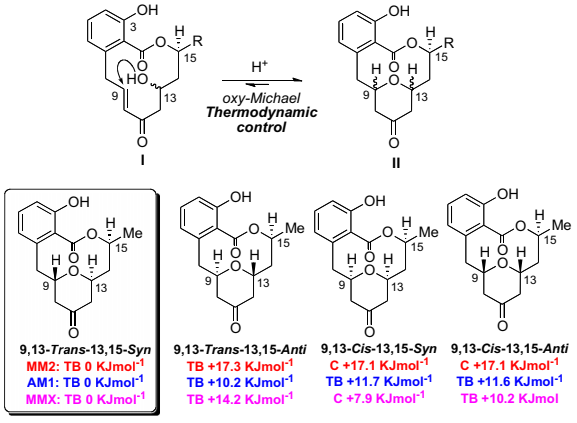
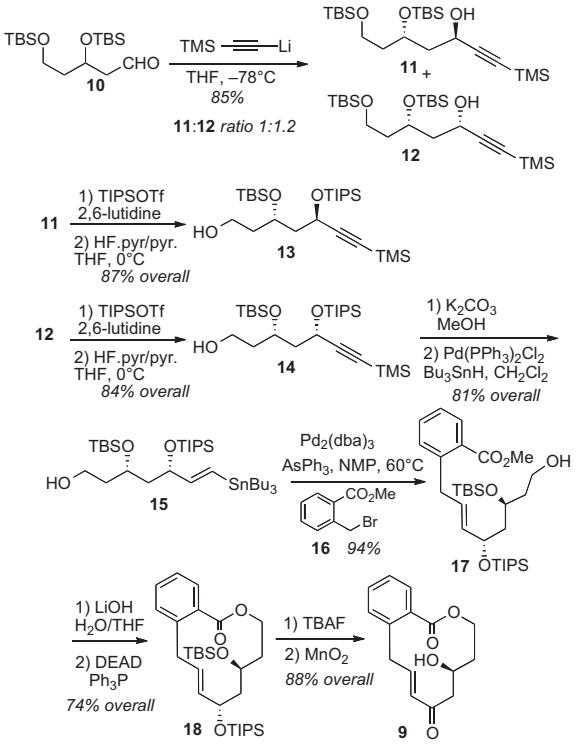


Fig. 2. Energy calculations for pyranone diastereoisomers.

2.1. Synthesis of a model transannular cyclisation precursor

In order to rapidly test the hypothesis detailed above, we synthesized a model enone cyclisation precursor **9** devoid of the C3 and C15 substituents (Scheme 2). The route began with the addition

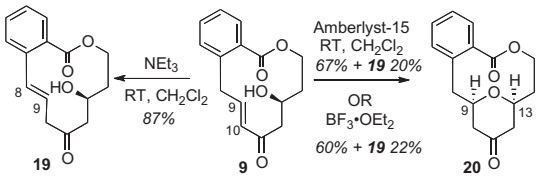


Scheme 2. Synthesis of model enone **9**.

of lithium TMS acetylide to known racemic aldehyde **10**[16] to afford the *anti*-alcohol **11** and the *syn*-isomer **12** as a 1:1.1 mixture (confirmed below), which was separated by flash chromatography. Each

of these isomers was then protected as the TIPS ether. Selective primary TBS group removal gave the alcohols **13** and **14** in good yields. We then proceeded with the *syn*-isomer **14** for the model study. Removal of the TMS group and Pd catalysed hydrostannylation[17] gave the stannane **15**. A highly efficient Stille cross coupling reaction[18,19] between the benzyl bromide **16**[20] and stannane **15** then gave the alkene **17** in excellent yield. The lactone was then formed by hydrolysis of the ester in **17** followed by Mitsunobu macrocyclisation[21] to give the lactone **18** in good yield. Removal of the protecting groups and selective allylic oxidation with MnO_2 gave the racemic enone **9** ready for cyclisation studies.

At the inception of this study, there were few examples of base or acid induced intramolecular 6-*endo*-*trig* type oxy-Michael reactions of enones to generate pyran-4-ones. In all cases, the major product was the *cis*-2,6-disubtituted pyranone.[22,23] Treatment of enone **9** with strong base (NaH, LiHMDS etc.) resulted only in decomposition. Exposure of **9** to mild base, such as NEt_3 gave a new compound, which was identified as the isomeric 8,9-alkene **19** whereupon the double bond had isomerised into conjugation with the aromatic ring. No cyclisation products were detected and so we turned to acidic conditions. Treatment of **9** with CSA or pTsOH did not induce cyclisation however, when enone **9** was exposed to Amberlyst-15 ion exchange resin[23] at rt, the *cis*-pyranone **20** was isolated in good yield along with isomerised alkene **19**. Treatment of **9** under Lewis acidic conditions ($BF_3{\cdot}Et_2O$) also gave the pyranones **20** and **19** in similar yields (Scheme 3).



Scheme 3. Cyclisation of enone **9** to *cis*-pyranone **20**.

The structure of **20** was assigned based on NMR analysis, in particular the NOE observed between H9 (3.98 ppm), and H13 (4.08 ppm). In addition, compound **20** was crystalline and a single crystal X-ray structure[12d] was determined, which confirmed the structure (Fig. 3). The pyranone ring adopts a chair-like conformation in both solution and solid state.

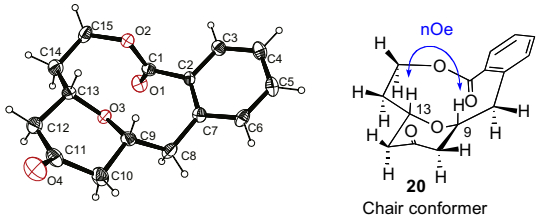


Fig. 3. X-ray structure of *cis*-pyranone **20** and NOE observed.

The NMR spectrum of the crude product from the above cyclisation showed a trace amount of another product tentatively assigned as the desired *trans*-pyranone. This suggested that the *cis*-isomer was the kinetic product and so we conducted the cyclisation in refluxing $CDCl_3$ (0.035 M) as solvent and monitored the reaction by ^1H NMR spectroscopy (see Fig. 4). After 3 h at reflux, the alkene isomer **19** and *cis*-pyranone **20** were the only products observed with only a trace amount of enone **9** remaining. After 7 h, the alkene **19** and *cis*-pyranone **20** began to disappear and two new compounds were formed. Eventually, after 22 h, only a trace of **20** remained and the two new compounds were identified as the desired *trans*-pyranone **21** and diene **22** after purification by flash chromatography (Scheme 4).

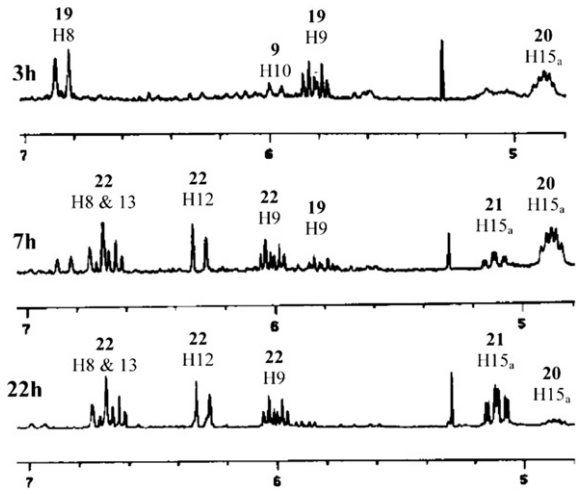
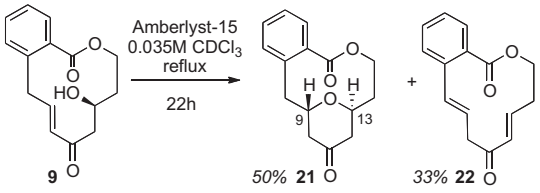


Fig. 4. ^1H NMR spectra of cyclisation reaction of enone **9** after refluxing with Amberlyst-15 in $CDCl_3$ for 3 h, 7 h and 22 h.



Scheme 4. Cyclisation of enone **9** to *trans*-pyranone **21**.

The diene **22** showed four signals in the alkene region assigned to H8, H9, H12 and H13 whilst the *trans*-pyranone **21** showed signals for H9 and H13 at δ 4.10 and 4.56 ppm, respectively.

The *trans*-pyranone **21** was also crystalline and a single crystal X-ray structure[12d] (Fig. 5) was determined, which confirmed the structure. In this case, the *trans*-pyranone ring was in a twist-boat conformation in the solid state. NOE studies also indicated that the pyranone ring was also in the twist-boat conformation in solution. These NMR observations were similar to those seen in the natural product **2** itself.[5]

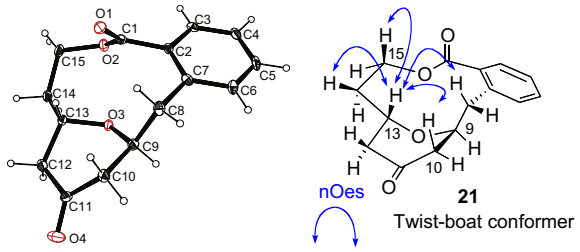
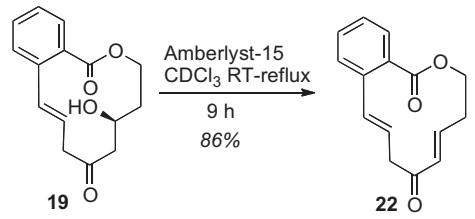


Fig. 5. X-ray structure of *trans*-pyranone **21** and NOEs observed.

The successful cyclisation of the enone **9** to the desired *trans*-pyranone **21** experimentally supported the original calculations that suggested a *trans*-pyranone as the most stable isomer. However the formation of the undesired diene was a problem. The diene **22** obviously arises from acid induced elimination of isomerised alkene **19**. However since **19** contains a vinylogous ester, cyclisation of this to a pyranone could also occur. However, heating a solution of **19** in a solution of $CDCl_3$ with Amberlyst-15 only produced diene

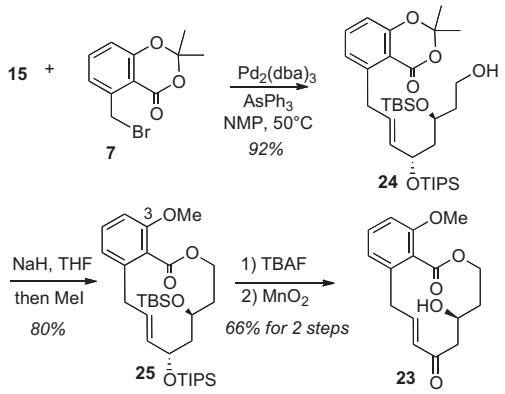
22 (Scheme 5). No cyclisation to a pyranone was observed and thus the isomerisation of enone **9** to **19** is an unproductive pathway.



Scheme 5. Conversion of alkene **19** to diene **22**.

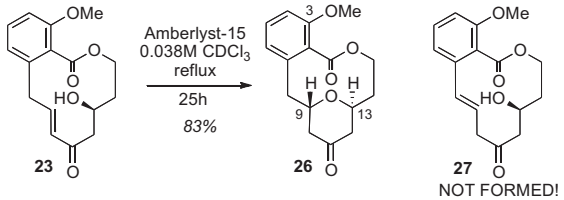
2.2. Model cyclisation with a C3 substituent

We next explored the influence of the C3 oxygen substituent on the aromatic ring. The requisite cyclisation precursor enone **23** was synthesized from stannane **15** as shown in Scheme 6. A Stille coupling between bromide **7**[14] and stannane **15** gave alkene **24** in excellent yield. Base induced macrolactonisation[12a,14] followed by in situ methylation of the resultant phenolate anion gave macrolactone **25**. In early studies, it was found a free phenol was detrimental to the cyclisation reaction so this was protected as a methyl ether. Silyl group removal followed by allylic oxidation yielded enone **23**.



Scheme 6. Synthesis of enone **23**.

Treatment of enone **23** with Amberlyst-15 in boiling $CDCl_3$ for 25 h resulted in the formation of *trans*-pyranone **26** with only a trace of the *cis*-isomer detected (Scheme 7).



Scheme 7. Cyclisation of enone **23** to *trans*-pyranone **26**.

The structure of *trans*-pyranone **26** was also confirmed by X-ray crystallography (Fig. 6).[12d] It is noteworthy that no C8–C9 alkene isomer **27** was produced in this case. The presence of the C3 OMe group is enough to reduce the C8 acidity and thwart any isomerisation of the alkene into conjugation with the aromatic ring. Alternatively, the OMe group may force the ester carbonyl out of planarity enough to reduce the C8 acidity. In any case, this study verified our approach and we next explored an approach to the fully substituted system.

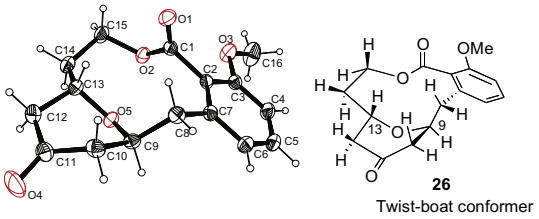
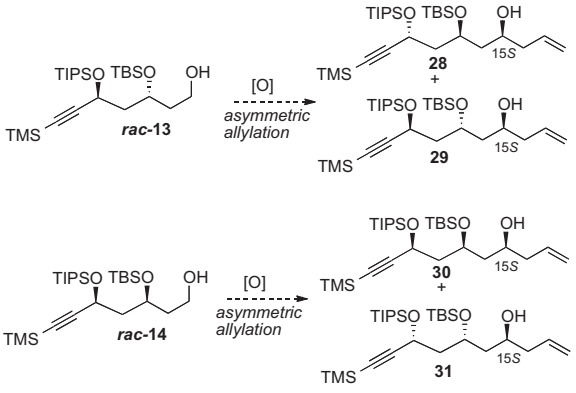


Fig. 6. X-ray structure of *trans*-pyranone **26**.

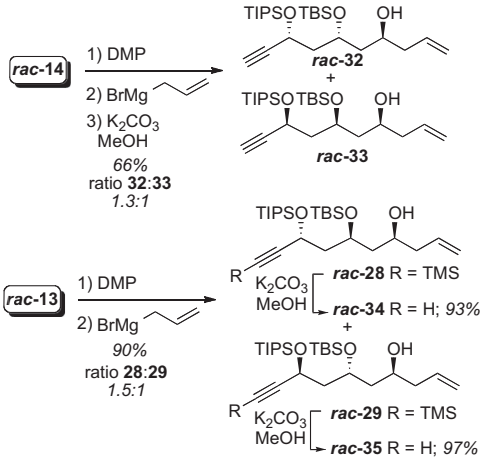
2.3. Addition of the C15 substituent

With the above results in hand, we next embarked on the synthesis of a fully substituted system. This required the installation of the C15 stereochemistry, which is hopefully the only stereocentre required for stereocontrol. Therefore, oxidation and asymmetric allylation of either the diastereoisomeric racemic alcohols *anti*-*rac*-**13** and *syn*-*rac*-**14** prepared earlier, would give an intermediate with the 15*S* stereochemistry required for the synthesis of the apicularen A (**1**) advanced intermediate **4**. As shown in Scheme 8, oxidation and asymmetric allylation of *rac*-**13** gives the 15*S* diastereoisomers *anti*,*syn*-**28** and *anti*,*anti*-**29**, which can both be used. The same applied for *rac*-**14**, which would afford 15*S* isomers *syn*,*syn*-**30** and *syn*,*anti*-**31**.



Scheme 8. Proposed synthesis of the 15*S* stereoisomers from *rac*-**13** and *rac*-**14**.

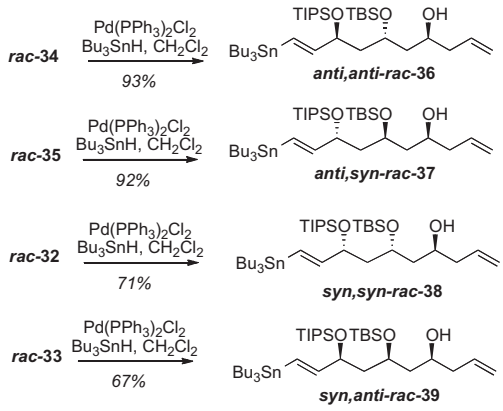
The racemic diastereoisomers where first synthesized from *rac*-**13** and *rac*-**14** as shown in Scheme 9. Oxidation of *rac*-**13** with Dess–Martin periodinane (DMP) followed by addition of allyl magnesium bromide at −78 °C gave the alcohols as an inseparable



Scheme 9. Synthesis of alcohols *rac*-**32**, *rac*-**33**, *rac*-**34** and *rac*-**35**.

mixture (~1.3:1). Removal of the TMS group then gave alcohols *rac*-**32** and *rac*-**33**, which could be separated by flash chromatography. On the other hand, oxidation of *rac*-**13** followed by Grignard addition gave the alcohols *rac*-**28** and *rac*-**29** (1.5:1 ratio), which were separable by flash chromatography. Deprotection of the alkynes *rac*-**28** and *rac*-**29** then afforded alcohols *rac*-**34** and *rac*-**35**, respectively. The stereochemistry of all these diastereoisomers arose from X-ray analysis of a latter intermediate (see below).

Hydrostannylation[17] of each of the diastereoisomers *rac*-**32**, *rac*-**33**, *rac*-**34** and *rac*-**35** proceeded in good yield to afford all the corresponding racemic stannanes *rac*-**38**, *rac*-**39**, *rac*-**36** and *rac*-**37** (Scheme 10). It is noteworthy that the hydrostannylation of *syn*,*anti*-*rac*-**32**, and *syn*,*syn*-*rac*-**33** diastereoisomers derived from *rac*-**14** gave lower yields.



Scheme 10. Synthesis of the stannane diastereoisomers *rac*-**36**, *rac*-**37**, *rac*-**38** and *rac*-**39**.

A Stille coupling between the stannane *rac*-**38** and benzyl bromide **7** gave the alkene *rac*-**40** in good yield. Macrolactonisation was achieved upon exposure of *rac*-**40** to NaH in THF to afford the macrolactone *rac*-**41**. Removal of the silyl protecting groups gave the triol *rac*-**42** as a solid, which provided crystals suitable for X-ray analysis. The X-ray structure[24] (Fig. 7) of *rac*-**42** allowed for the assignment of the stereochemistry for *rac*-**38** and *rac*-**39** as well as the original alkynes *anti*-**13** and *syn*-**14** (Scheme11).

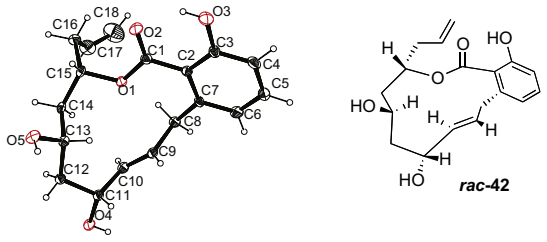
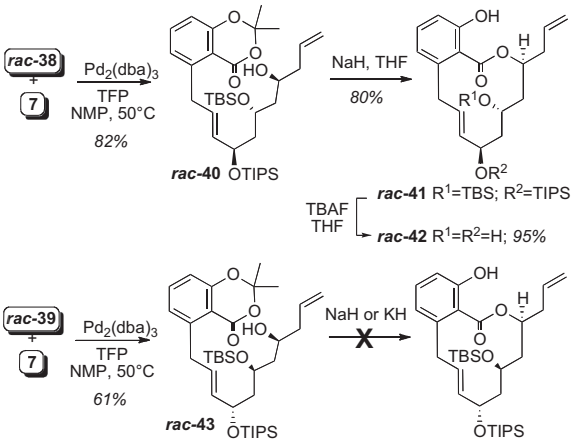


Fig. 7. X-ray structure of macrolactone triol *rac*-**42**.

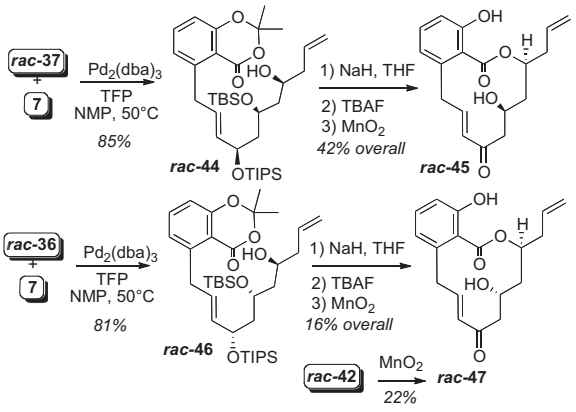
Coupling between *rac*-**39** and **7** gave *rac*-**43** in a lower yield than the previous case. More importantly, all attempts at base induced cyclisation of *rac*-**43** failed indicating that the relative configuration in this compound is not conducive to macrolactone formation.

The stereochemistry of each of the *anti*-**13** derived stannanes *rac*-**36** and *rac*-**37** was confirmed as shown in Scheme 12. Stille coupling of *rac*-**37** with benzyl bromide **7** gave alkene *rac*-**44**, which smoothly underwent macrolactonisation upon exposure to NaH. Treatment with TBAF and allylic oxidation gave enone *rac*-**45**. Stille coupling between the *anti*,*anti*-stannane *rac*-**35** and bromide **7**



Scheme 11. Synthesis of macrolactone triol *rac*-**42**.

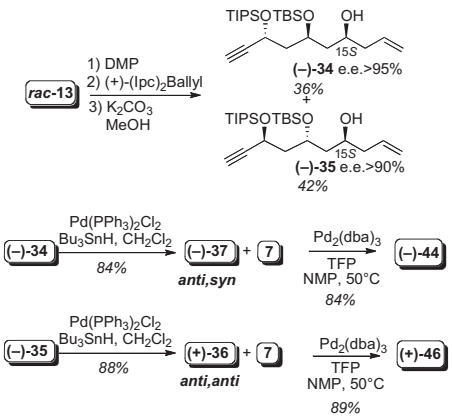
gave the alkene *rac*-**46** in good yield. Macrolactonisation, deprotection and oxidation then yielded enone *rac*-**47** in low yield. Similarly, oxidation of macrolactone triol *rac*-**42** gave the same diastereoisomer *rac*-**47**.



Scheme 12. Synthesis of enone diastereoisomers *rac*-**45** and *rac*-**47**.

2.4. Formal total synthesis of (−)-apicularen A

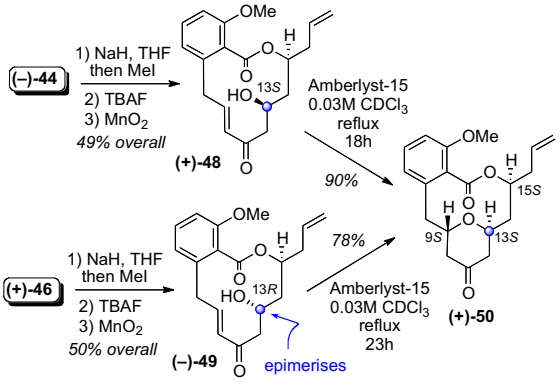
From the results obtained above, we decided to utilize *anti*-alcohol *rac*-**13** for the asymmetric allylation reaction required for the enantioselective synthesis the of apicularen A intermediate **4** (Scheme 13). Thus, Brown asymmetric allylation[16,25] of the aldehyde derived from *rac*-**13** followed by TMS group removal afforded



Scheme 13. Synthesis of alkene diastereoisomers (−)-**44** and (+)-**46**.

the alkynes (−)-**34** and (−)-**35** in 36% and 42% yields, respectively. The optical purity of each of these was assessed by their conversion to the (*S*)-Mosher esters. ^{1}H NMR analysis of the crude Mosher esters indicated that each isomer was obtained in >90 ee. Hydrostannylation[17] of both (−)-**34** and (−)-**35** afforded the optically active stannanes (−)-**37** and (+)-**36**.

The Stille coupling between (+)-**36** and (−)-**37** and the benzyl bromide then provided the alkenes (+)-**46** and (−)-**44** in excellent yields. Because of issues encountered with the free phenol during the model studies, the transannular cyclisations were conducted on the methyl ethers as shown in Scheme 14. Macrolactonisation of (−)-**44** and methylation of the intermediate phenolate anion gave the macrolactone, which was desilylated and oxidized to the enone (+)-**48**. Similarly, macrolactonisation of (+)-**46** followed by deprotection and allylic oxidation yielded isomer (−)-**49**. Treatment of a 0.03 M solution of (+)-**48** in $CDCl_3$ with Amberlyst-15 gave the desired *trans*-pyranone (+)-**50** with the correct 9,13-*trans*-13,15-*syn* absolute stereochemistry. More importantly, as predicted, cyclisation of the C13 epimer (−)-**49** in refluxing $CDCl_3$ for a longer period gave the same *trans*-pyranone (+)-**50** as the major isomer (>10:1 *trans*:*cis*) in a lower yield. Monitoring of this reaction by ^{1}H NMR spectroscopy showed a complex mixture after 2 h reflux. This mixture eventually resolved to one major compound (+)-**50**. Thus the C13 stereochemistry fully epimerizes to the correct configuration and this outcome is controlled by the C15 stereocentre.



Scheme 14. Synthesis of *trans*-pyranone (+)-**50**.

trans-Pyranone (+)-**50** was also crystalline and the structure was confirmed by X-ray crystallography (Fig. 8).[11c] In addition, (+)-**50** showed similar NOEs to that seen in the natural product **1**. Taylor and co-workers also reported a synthesis of (−)-**50** during their formal total synthesis of apicularen A (**1**).[11b] The data reported for this compound matched our material except for the sign of optical rotation {$[\alpha]_{D16}$ +138 (*c* 0.253, $CHCl_3$), lit.[11b] $[\alpha]_{D22}$ −140 (*c* 0.60, $CHCl_3$)} also confirming we had synthesized the correct enantiomer.

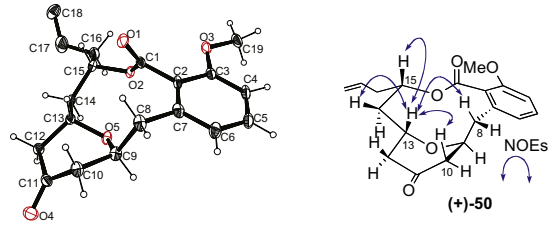
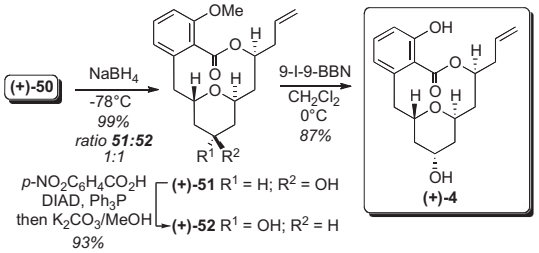


Fig. 8. X-ray structure of *trans*-pyranone (+)-**50** and NOEs observed.

The final steps to key intermediate **4** are shown in Scheme 15. Selective reduction of the ketone in (+)-**50** proved challenging with all reagents trialed giving essentially 1:1 mixtures. This could be attributed to the twist-boat conformation of the *trans*-pyranone ring offering little steric difference between the two faces of the carbonyl group. In any event, the two isomeric alcohols (+)-**51** and (+)-**52** could be separated and the physical data for the latter compound compared well with that reported by Taylor and co-workers.[11b] The incorrect isomer (+)-**51** could easily be converted in the desired alcohol (+)-**52** by a simple Mitsunobu inversion[20] in high yield. Demethylation of (+)-**52** then gave the target compound (+)-**4** the data for which matched that reported in the literature {$[\alpha]_{D17}$ +5.6 (*c* 0.41, MeOH), lit.[10a] $[\alpha]_{D22}$ +6.8 (*c* 0.16, MeOH) lit.[11a] $[\alpha]_{D22}$ +5 (*c* 0.03, MeOH), lit. (enantiomer)[11b] $[\alpha]_{D20}$ −4.5 (*c* 0.15, MeOH)}.



Scheme 15. Completion of the synthesis of apicularen intermediate (+)-**4**.

3. Conclusion

In conclusion, we have achieved the synthesis of key apicularen A (**1**) intermediate **4**, which constitutes formal total synthesis of this natural product. The approach utilized a novel transannular 6-*endo*,*trig* oxy-Michael reaction under thermodynamic control to form the *trans*-tetrahydropyran ring in which the only stereocontrolling element is the 15*S* stereocentre. The facile nature of this transannular cyclisation coupled with the observation that the C13 stereochemistry can be epimerized from the salicylihalamide configuration to the apicularen one lends support to the idea that this ring forming reaction may be utilized in the biogenesis of this interesting natural product. We envisage this methodology could be applied to the synthesis of other macrolactone-2,6-disubstituted tetrahydropyran containing natural products.[26]

4. Experimental

4.1. General

Unless otherwise stated, ^{1}H NMR (300 MHz or 400 MHz) and proton decoupled ^{13}C NMR spectra (75.5 MHz or 100 MHz) were recorded for deuterochloroform solutions with residual chloroform as internal standard. Optical rotations were recorded in a 10 cm microcell. Infrared spectra were recorded using a Bio-Rad FTS165 FT-IR spectrometer. Ultraviolet spectra were recorded using a Shimadzu UV-2401PC spectrophotometer. HRMS (ESI) mass spectra were run on a Bruker 4.7T BiOAPEX FTMS mass spectrometer at Monash University, Clayton, Victoria. Flash chromatography was carried out on Merck silica gel 60. Anhydrous THF was distilled from sodium metal/benzophenone under a nitrogen atmosphere. All other anhydrous solvents were purified according to standard methods. Petrol refers to petroleum ether boiling between 40 and 60 °C.

*4.1.1. Alkynes anti-**11** and syn-**12**.* To a stirred solution of trimethylsilylacetylene (6.2 mL, 22.0 mmol) in THF (126 mL) at −78 °C

was added dropwise a solution of ^{n}BuLi (15.8 mL, 39.6 mmol, 2.5 M in hexanes). After stirring at −78 °C for 30 min, a solution of the known aldehyde **10**[16] (7.61 g, 22.0 mmol) in THF (80 mL) was slowly added dropwise via cannula. The reaction mixture was stirred at −78 °C for 15 min and then at rt for a further 20 min. The solution was diluted with Et_2O, followed by the slow addition of cold saturated aqueous NH_4Cl. The usual workup produced a residue, which was purified by flash chromatography using 2.5% EtOAc/petrol as eluent to afford the racemic *anti*-alkyne **11** (3.32 g, 34%) as a pale yellow oil: IR ν_{max} (film) 3435 (O–H), 2958, 2931, 2897, 2888, 2859, 2172 (C≡C), 1253, 1098, 839 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.04 (s, 6H, SiMe), 0.09 (s, 3H, SiMe), 0.13 (s, 3H, $SiMe_2$), 0.16 (s, 9H, $SiMe_3$), 0.88 (s, 9H, $SiCMe_3$), 0.89 (s, 9H, $SiCMe_3$), 1.65–1.85 (m, 2H, H6), 1.86–2.00 (m, 2H, H4), 3.65 (t, *J*=6.6 Hz, 2H, H7), 4.24 (quint, *J*=6.6 Hz, 1H, H5), 4.60 (dd, *J*=8.1, 3.3 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ −5.4, −4.6, −4.5, −0.1, 17.9, 18.2, 25.8, 25.9, 39.7, 42.8, 59.3, 60.4, 68.2, 88.7, 106.7; HRMS (ESI) calcd for $C_{22}H_{48}O_3Si_3Na$ [M+Na$^+$]: 467.2809, found: 467.2802.

Further elution afforded a fraction of mixed TMS alkynes **11** and **12** (1.83 g, 19%). Further elution then TMS *syn*-alkyne **12** (4.30 g, 44%) as a pale yellow oil: IR ν_{max} (film) 3421(O–H), 2958, 2931, 2897, 2888, 2859, 2173 (C≡C), 1252, 1101, 839 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.05 (s, 6H, $SiMe_2$), 0.08 (s, 3H, SiMe), 0.10 (s, 3H, $SiMe_2$), 0.16 (s, 9H, $SiMe_3$), 0.88 (s, 9H, $SiCMe_3$), 0.89 (s, 9H, $SiCMe_3$), 1.58 (br s, 1H, O*H*), 1.69–1.84 (m, 2H, H6), 1.89 (t, *J*=6.6 Hz, 2H, H4), 3.65–3.70 (m, 2H, H7), 4.08 (m, 1H, H5), 4.54 (t, *J*=6.6 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ −5.4, −4.7, −4.4, −0.2, 17.9, 18.2, 25.8, 25.9, 40.6, 44.1, 59.4, 61.3, 68.5, 89.4, 108.6; HRMS (ESI) calcd for $C_{22}H_{48}O_3Si_3Na$ [M+Na$^+$]: 467.2809, found: 467.2805.

*4.1.2. anti-Alcohol **13**.* To a stirred solution of alcohol **11** (4.87 g, 0.011 mol) and 2,6-lutidine (2.24 mL, 0.019 mol) in dichloromethane (167 mL) at 0 °C was added dropwise TIPSOTf (3.38 mL, 0.013 mmol). After stirring for 2 h at 0 °C, the usual pyridine workup gave a residue, which was purified by flash chromatography using 2.5% EtOAc/petrol as eluent to yield the TIPS ether (6.37 g, 97%) as a colourless oil: IR ν_{max} (film) 2958, 2931, 2895, 2867, 2173 (C≡C), 1252 (C–O), 1102, 1038, 839 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.04 (s, 6H, $SiMe_2$), 0.07 (s, 3H, SiMe), 0.08 (s, 3H, SiMe), 0.14 (s, 9H, $SiMe_3$), 0.885 (s, 9H, $SiCMe_3$), 0.89 (s, 9H, $SiCMe_3$), 1.06–1.37 (m, 21H, $Si(CHMe_2)_3$), 1.61–1.78 (m, 2H, H6), 1.83–1.94 (m, 2H, H4), 3.62–3.75 (m, 2H, H7), 4.01 (m, 1H, H5), 4.60 (dd, *J*=7.2, 6.6 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ −5.3, −5.28, −4.6, −4.3, −0.3, 12.5, 18.1, 18.14, 18.3, 25.9, 26.0, 40.4, 47.1, 59.8, 60.4, 66.4, 89.0, 107.8; HRMS (ESI) calcd for $C_{31}H_{68}O_3Si_4Na$ [M+Na$^+$]: 623.4143, found: 623.4157.

To a stirred solution of HF·pyridine (4.23 g, 138 mmol) and THF (130 mL) under argon was added pyridine (8.9 mL, 110 mmol) and the resulting solution was then added into a solution of the above TBS ether (6.37 g, 11 mmol) in THF (87 mL). After stirring for 20 h at 0 °C, Et_2O and saturated aqueous $NaHCO_3$ were added. The usual workup gave a residue, which was purified by flash chromatography using 5% EtOAc/petrol as eluent to yield the alcohol **13** [3.021 g, 90% based on recovered starting material (2.23 g)] as a colourless oil: IR ν_{max} (film) 3452 (O–H), 2959, 2894, 2888, 2868, 2172 (C≡C), 1251 (C–O), 1101, 1058, 842 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.11 (s, 6H, $SiMe_2CMe_3$), 0.14 (s, 9H, $SiMe_3$), 0.89 (s, 9H, $SiMe_2CMe_3$), 1.04–1.25 (m, 21H, $Si(CHMe_2)_3$), 1.49 (br s, 1H, O*H*), 1.71 (m, 1H, H2), 1.92 (m, 1H, H2), 1.98 (t, *J*=5.1 Hz, 2H, H4), 3.74 (ddd, *J*=8.4, 4.2, 3.9 Hz, 1H, H1), 3.88 (ddd, *J*=8.4, 6.3, 3.3 Hz, 1H, H1), 4.17 (m, 1H, H3), 4.41 (t, *J*=5.1 Hz, 1H, H5); ^{13}C NMR (75 MHz) δ −4.8, −4.4, −0.4, 12.3, 17.9, 18.0, 25.8, 37.7, 45.4, 60.2, 60.4, 69.1, 89.5, 107.1; HRMS (ESI) calcd for $C_{25}H_{54}O_3Si_3Na$ [M+Na$^+$]: 509.3278, found: 509.3268.

*4.1.3. syn-Alcohol **14**.* Alcohol **12** (360 mg, 0.81 mmol) was converted into the TIPS ether in the same manner as the above procedure to give a colourless oil (459 mg, 94%): ^{1}H NMR (300 MHz) δ 0.04 (s, 6H, $SiMe_2$), 0.06 (s, 3H, SiMe), 0.08 (s, 3H, SiMe), 0.14 (s, 9H, $SiMe_3$), 0.88 (s, 9H, $SiCMe_3$), 0.89(s, 9H, $SiCMe_3$), 1.06–1.35 (m, 21H, $Si(CHMe_2)_3$), 1.67–1.77 (m, 2H, H6), 1.78–1.99 (m, 2H, H4), 3.66 (app t, *J*=6.6 Hz, 2H, H7), 4.04 (m, 1H, H5) 4.60 (dd, *J*=8.8, 5.6 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ −5.4, −5.3, −4.6, −4.5, −0.2, 12.2, 17.7, 18.0, 18.2, 25.9, 26.0, 41.1, 46.1, 59.4, 61.6, 66.9, 89.4, 107.5; HRMS (ESI) calcd for $C_{31}H_{68}O_3Si_4Na$ [M+Na$^+$]: 623.4143, found: 623.4152.

Selective deprotection of the above ether (6.88 g, 0.012 mmol) was performed using the procedure described above. Purification by flash chromatography with 5–10% EtOAc/petrol as eluent afforded the alcohol **14** (4.31 g, 89% based on recovered starting material (900 mg)) as a colourless oil: ^{1}H NMR (300 MHz) δ 0.10 (s, 6H, $SiMe_2$), 0.14 (s, 9H, $SiMe_3$), 0.88 (s, 9H, $SiCMe_3$), 1.05–1.15 (m, 21H, $Si(CHMe_2)_3$), 1.71 (m, 1H, H2), 1.84 (m, 1H, H2), 1.90–2.02 (m, 2H, H4), 2.43 (br s, 1H, O*H*), 3.72 (br m, 1H, H1), 3.85 (m, 1H, H1), 4.19 (m, 1H, H3), 4.54 (dd, *J*=7.8, 5.7 Hz, 1H, H5); ^{13}C NMR (75 MHz) δ −4.7, −4.6, −0.3, 12.2, 17.9, 18.0, 25.8, 38.5, 44.9, 59.9, 61.4, 86.9, 89.7, 107.1; HRMS (ESI) calcd for $C_{25}H_{54}O_3Si_3Na$ [M+Na$^+$]: 509.3278, found: 509.3277.

*4.1.4. Stannane **15**.* To a stirred solution of the TMS acetylene **14** (2.02 g, 4.15 mmol) in methanol (22 mL) was added K_2CO_3 (577 mg, 4.15 mmol). After stirring for 2 h at rt, the solvent was removed under reduced pressure and the usual workup followed by purification of the crude product by flash chromatography using 5% EtOAc/petrol as eluent yielded the alkyne (1.66 g, 97%) as a pale yellow oil: IR ν_{max} (film) 3447 (O–H), 3312, 2947, 2893, 2868, 2114 (C≡C), 1257 (C–O), 1102, 1062, 837 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.10 (s, 3H, SiMe), 0.11 (s, 3H, SiMe), 0.89 (s, 9H, $SiCMe_3$), 1.06–1.09 (m, 21H, $Si(CHMe_2)_3$), 1.72 (ddd, *J*=14.4, 10.2, 4.8 Hz, 1H, H2), 1.88–2.06 (m, 3H, H2, H4), 2.26 (t, *J*=4.2 Hz, 1H, O*H*), 2.44 (d, *J*=2.1 Hz, 1H, H7), 3.72 (m, 1H, H1), 3.88 (m, 1H, H1), 4.19 (m, 1H, H3), 4.57 (ddd, *J*=7.8, 4.5, 2.1 Hz, 1H, H5); ^{13}C NMR (75 MHz) δ −4.7, −4.6, 12.2, 17.8, 17.96, 18.0, 25.8, 38.7, 45.4, 59.8, 60.9, 68.6, 73.1, 85.2; HRMS (ESI) calcd for $C_{22}H_{46}O_3Si_2Na$ [M+Na$^+$]: 437.2883, found: 437.2889.

To a stirred solution of the above alkyne (1.00 g, 2.42 mmol) in CH_2Cl_2 (24 mL) at 0 °C was added $Pd(PPh_3)_2Cl_2$ (270 mg, 0.24 mmol). After stirring for 10 min at 0 °C, Bu_3SnH (1.62 mL, 6.0 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min, then it was filtered through Celite and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography using 1% NEt_3/2.5–5% EtOAc/petrol as eluent afforded the vinyl stannane **15** (1.43 g, 84%) as a light yellow oil: IR ν_{max} (film) 3384 (O–H), 27,958, 2929, 2868, 1255 (C–O), 1094, 1055, 994, 883 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.08 (s, 3H, SiMe), 0.09 (s, 3H, $SiMe_2CMe_3$), 0.85–0.90 (m, 15H, Sn*Bu*$_3$), 0.89 (s, 9H, $SiCMe_3$), 1.04 (s, 21H, $Si(CHMe_2)_3$), 1.24–1.36 (m, 6H, Sn*Bu*$_3$), 1.42–1.53 (m, 6H, Sn*Bu*$_3$), 1.66–1.73 (m, 2H, H2), 1.83–1.98 (m, 2H, H4), 2.61 (br s, 1H, O*H*), 3.71 (m, 1H, H1), 3.85 (br m, 1H, H1), 4.06 (br m, 1H, 3), 4.24 (app q, *J*=6.3 Hz, 1H, H5), 5.93 (dd, *J*=19.2, 6.3 Hz, 1H, H6), 6.07 (d, *J*=19.2 Hz, 1H, H7); ^{13}C NMR (75 MHz) δ −4.6, −4.4, 9.4, 12.5, 13.7, 17.9, 18.2, 25.8, 27.3, 29.1, 38.0, 45.2, 60.3, 69.5, 74.6, 128.1, 151.3; HRMS (ESI) calcd for $C_{34}H_{74}O_3Si_2SnNa$ [M+Na$^+$]: 727.4096, found: 727.4093.

*4.1.5. Alkene **17**.* A solution of vinyl stannane **15** (40 mg, 56.7 μmol) and the benzyl bromide **16** (17 mg, 73.7 μmol) in NMP (420 μL) was freeze/thaw degassed twice. The catalyst $Pd_2(dba)_3$ (2.5 mg, 2.9 μmol) and triphenylarsine (3.5 mg, 11.3 μmol) were then added and the reaction mixture was freeze/thaw degassed once more. After stirring overnight at 60 °C, the reaction mixture was diluted with Et_2O and washed with aqueous ammonium hydroxide solution. The aqueous phase was separated, extracted with Et_2O and the organic fractions were then combined, dried

($MgSO_4$) and the solvent was removed. The crude product was purified by flash chromatography with 5% EtOAc/petrol as eluent to give the alkene **17** (30 mg, 94%) as a colourless oil: IR ν_{max} (film) 3439 (O–H), 3064, 3026 (C=C–H), 2947, 2893, 2866, 1726 (O=C–O), 1602, 1577, 1259 (C–O), 1082, 1064, 974 (C=C), 883 cm^{-1}; ^1H NMR (300 MHz) δ −0.10 (s, 3H, SiMe), 0.04 (s, 3H, SiMe), 0.86 (s, 9H, $SiCMe_3$), 0.98 (s, 21H, $Si(CHMe_2)_3$), 1.59–1.70 (m, 2H, H7′), 1.79–1.88 (m, 2H, H5′), 2.02 (br s, 1H, O*H*), 3.66 (m, 1H, H1′), 3.72 (t, *J*=6.3 Hz, 2H, H8′), 3.81 (m, 1H, H1′), 3.88 (s, 3H, OCH_3), 3.99 (quint, *J*=6.0 Hz, 1H, H6′), 4.25 (app q, *J*=6.9 Hz, 1H, H4′), 5.40 (dd, *J*=15.5, 7.5 Hz, 1H, H3′), 5.77 (dt, *J*=15.5, 6.6 Hz, 1H, H2′), 7.23–7.29 (m, 2H, H3, H5), 7.43 (dt, *J*=7.5, 1.2 Hz, 1H, H4), 7.88 (dd, *J*=7.8, 1.2 Hz, 1H, H6); ^{13}C NMR (75 MHz) δ −4.6, −4.5, 12.4, 18.0, 18.1, 25.8, 36.8, 38.4, 45.8, 51.9, 60.1, 68.9, 71.2, 126.2, 129.3, 129.6, 130.7, 131.0, 132.1, 134.5, 141.7, 167.9; HRMS (ESI) calcd for $C_{31}H_{56}O_4Si_2Na$ [M+Na^+]: 587.3564, found: 587.3569.

4.1.6. Lactone ***18***. To a stirred solution of $LiOH\cdot H_2O$ (250 mg, 5.74 mmol) in water (6 mL) was added THF (8 mL) and then methanol was added dropwise until one phase was obtained. The resulting homogeneous solution was added to the ester **17** (325 mg, 574 μmol). The solution was stirred overnight at rt and the solvent was then removed. Ethyl acetate and water were added and the mixture was cooled to 0 °C, then acidified with 10% aqueous HCl to pH 3. The usual workup afforded the crude seco acid (300 mg), which was used without further purification. To a stirred mixture of the crude secoacid (300 mg, 0.54 mmol) and PPh_3 (186 mg, 826 μmol) in benzene (11.7 mL) was added DEAD (117 μL, 826 μmol) dropwise over a period of 5 min at rt. After stirring the reaction mixture overnight at rt, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel using 1–5% EtOAc/petrol as eluent to yield the lactone **18** (250 mg, 86%) as a colourless oil: IR ν_{max} (film) 3073 (C=C–H), 2948, 2930, 2894, 2866, 1725 (O=C–O), 1602 (Ar), 1578 (Ar), 1266 (C–O), 1080, 977, 884 cm^{-1}; ^1H NMR (300 MHz) δ −0.10 (s, 3H, $SiMe_2CMe_3$), −0.07 (s, 3H, $SiMe_2CMe_3$), 0.83 (s, 9H, $SiMe_2CMe_3$), 1.03 (s, 21H, $Si(CHMe_2)_3$), 1.67–2.04 (m, 4H, H12, H14), 3.27 (br d, *J*=14.4 Hz, 1H, H8), 3.42 (quint, *J*=5.4 Hz, 1H, H13), 3.95 (dd, *J*=14.4, 9.6 Hz, 1H, H8), 3.99–4.11 (m, 2H, H11, H15), 4.72 (ddd, *J*=11.4, 8.4, 3.0 Hz, 1H, H15), 5.20 (ddd, *J*=15.6, 9.6, 3.3 Hz, 1H, H10), 5.37 (ddd, *J*=15.6, 8.7, 1.2 Hz, 1H, H9), 7.17–7.28 (m, 2H, H4, H6), 7.37 (t, *J*=7.5 Hz, 1H, H5), 7.45 (d, *J*=7.8 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ −4.6, −4.5, 12.3, 17.8, 18.0, 18.1, 25.7, 37.2, 37.4, 46.0, 61.8, 65.4, 72.5, 126.3, 128.0, 128.6, 130.4, 130.6, 133.6, 136.2, 138.9, 168.8; HRMS (ESI) calcd for $C_{30}H_{52}O_4Si_2Na$ [M+Na^+]: 555.3302, found: 555.3303.

4.1.7. Enone ***9***. To a stirred solution of lactone **18** (20 mg, 0.041 mmol) in THF (1.5 mL) was added TBAF (81 mg, 0.25 mmol) and the resulting solution was stirred for two days at rt. Ethyl acetate and water were added and the product was extracted into ethyl acetate washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on silica gel using 80% EtOAc/petrol as eluent to give the diol (10 mg, 94%) as a colourless crystalline solid: mp 163–164 °C; IR ν_{max} (film) 3393 (O–H), 2947, 2925, 1723 (O=C–O), 1601 (Ar), 1559 (Ar), 1276 (C–O), 1133 (C–O), 1081 (C–O), 980 cm^{-1}; ^1H NMR (300 MHz) δ 1.62 (br s, 1H, O*H*), 1.66 (br s, 1H, O*H*), 1.79 (ddd, *J*=13.5, 10.5, 5.1 Hz, 1H, H14), 1.86–1.93 (m, 2H, H12, H14), 2.10 (ddd, *J*=14.7, 7.2, 3.0 Hz, 1H, H12), 3.27 (d, *J*=14.4 Hz, 1H, H8), 3.51 (app quint, *J*=5.4 Hz, 1H, H13), 3.94 (dd, *J*=14.4, 9.0 Hz, 1H, H8), 4.05–4.15 (m, 2H, H11, H15), 4.76 (ddd, *J*=11.4, 8.1, 3.0 Hz, 1H, H15), 5.41–5.45 (m, 2H, H9, H10), 7.21–7.29 (m, 2H, H4, H6), 7.38 (ddd, *J*=7.5, 7.5, 1.2 Hz, 1H, H5), 7.43 (dd, *J*=7.5, 1.2 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ 37.0, 37.2, 44.2, 61.7, 65.3, 72.5, 126.5, 127.9, 130.5, 130.8, 130.9, 133.5, 134.6, 138.4, 168.8; HRMS (ESI) calcd for $C_{15}H_{18}O_4Na$ [M+Na^+]: 285.1103, found: 285.1109.

To a stirred solution of the above diol (15 mg, 0.057 mmol) in CH_2Cl_2 (2 mL) was added MnO_2 (90 mg, 1.14 mmol). The resulting mixture was stirred overnight at rt, then diluted with CH_2Cl_2 and filtered through Celite. Removal of the solvent under reduced pressure and purification of the crude residue by flash chromatography using 60% EtOAc/petrol as eluent afforded the enone **9** (14 mg, 94%) as a colourless thin film: IR ν_{max} (film) 3445 (O–H), 3057 (C=C–H), 2963, 1724 (O=C–O), 1691 (C=O) 1623 (C=C), 1601 (Ar), 1273, 1079 (C–O), 977, 832 cm^{-1}; ^1H NMR (400 MHz) δ 1.76 (dddd, *J*=15.6, 6.4, 4.8, 1.3 Hz, 1H, H14), 2.04 (m, 1H, H14), 2.59 (dd, *J*=14.0, 9.6 Hz, 1H, H12), 2.82 (dd, *J*=14.0, 4.4 Hz, 1H, H12), 3.52 (ddd, *J*=18.8, 4.0, 2.0 Hz, 1H, H8), 4.12–4.31 (m, 3H, H8, H13, H15), 4.69 (br s, 1H, O*H*) 4.73 (ddd, *J*=11.2, 4.4, 3.6 Hz, 1H, H15), 5.98 (dt, *J*=16.0, 1.6 Hz, 1H, H10), 6.85 (ddd, *J*=16.0, 6.0, 4.0 Hz, 1H, H9), 7.24 (d, *J*=7.6 Hz, 1H, H6), 7.35 (br t, *J*=7.2 Hz, 1H, H4), 7.44 (dt, *J*=7.6, 1.6 Hz, 1H, H5), 7.55 (dd, *J*=7.6, 1.2 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ 34.7, 36.4, 49.4, 62.3, 66.5, 127.1, 128.2, 130.3, 131.2, 131.3, 133.2, 136.4, 145.2, 169.1, 199.7; HRMS (ESI) calcd for $C_{15}H_{16}O_4Na$ [M+Na^+]: 283.0946, found: 283.0940.

4.1.8. Isomerised alkene ***19***. To a solution of the enone **9** (14 mg, 0.054 mmol) in CH_2Cl_2 (3 mL) was added 3 drops of triethylamine. After stirring overnight at rt, the solvents were removed to give the crude product, which, was purified by flash chromatography using 60% EtOAc/petrol as eluent to give the isomerised alkene **19** (12 mg, 86%) as a colourless thin film; IR ν_{max} (film) 3409 (O–H), 3055 (C=C–H), 2989, 2930, 1708 (O=C–O), 1657 (C=O), 1632 (Ar–C=C), 1266 (C–O), 978, 879 cm^{-1}; ^1H NMR (400 MHz) δ 2.09–2.16 (m, 2H, H14), 2.94 (dd, *J*=16.8, 4.5 Hz, 1H, H12), 3.03 (d, *J*=7.5 Hz, 1H, O*H*), 3.12 (dd, *J*=16.8, 5.4 Hz, 1H, H12), 3.24 (br d, *J*=6.6 Hz, 2H, H10), 4.14 (m, 1H, H13), 4.24 (ddd, *J*=11.7, 7.8, 3.9 Hz, 1H, H15), 4.60 (ddd, *J*=11.7, 6.0, 3.6 Hz, 1H, H15), 5.81 (dt, *J*=16.4, 6.6 Hz, 1H, H9), 6.85 (d, *J*=16.4 Hz, 1H, H8), 7.30 (br d, *J*=7.8 Hz, 1H, H6), 7.36 (dt, *J*=7.8, 1.2 Hz, 1H, H4), 7.50 (dt, *J*=7.8, 1.5 Hz, 1H, H5), 7.93 (dd, *J*=7.8, 1.2 Hz, 1H, H3); ^{13}C NMR (75 MHz) δ 34.7, 45.3, 46.5, 62.3, 68.5, 123.6, 127.6, 128.1, 129.1, 131.0, 132.3, 136.3, 138.4, 168.0, 209.4; HRMS (ESI) calcd for $C_{15}H_{16}O_4Na$ [M+Na^+]: 283.0946, found: 283.0948.

4.1.9. cis-Pyranone ***20***. *Method A*: To a stirred solution of enone **9** (15 mg, 0.058 mmol) in deuterochloroform (2 mL) was added Amberlyst-15 resin (4 mg) and the resulting mixture was left stirring overnight at rt. The mixture was filtered and the solvent was removed under reduced pressure. Purification of the crude residue on silica gel using 30% EtOAc/petrol as eluent yielded the *cis*-pyranone **20** (10 mg, 67%) as a colourless crystalline solid. Further elution gave the isomerised alkene **19** (3.0 mg, 20%).

Method B: To a stirred solution of enone **9** (6 mg, 0.023 mmol) in dichloromethane (1 mL) was added $BF_3\cdot OEt_2$ (15 μL) in dichloromethane (30 μL) at −78 °C. The resulting mixture was warmed to 0 °C and after stirring for 1 h, it was further warmed to rt. After stirring 47 h at rt, aqueous $NaHCO_3$ and EtOAc were added and the usual workup gave a crude product, which was purified on silica gel using 30% EtOAc/petrol as eluent to give the *cis*-pyranone **20** (3.6 mg, 60%) as a colourless crystalline solid: mp 140–141 °C; IR ν_{max} (film) 3056 (C=C–H), 2987, 2965, 2926, 1720 (C=O), 1603 (Ar), 1266 (C–O), 1085, 1077 (C–O), 896 cm^{-1}; ^1H NMR (300 MHz) δ 1.95–2.02 (m, 2H, H14), 2.42 (dd, *J*=15.6, 13.8 Hz, 1H, H10), 2.43 (d, *J*=15.9 Hz, 1H, H12), 2.60 (dd, *J*=15.9, 11.1 Hz, 1H, H12), 2.68 (dd, *J*=15.6, 3.9 Hz, 1H, H10), 2.88 (dd, *J*=15.2, 1.8 Hz, 1H, $H8_b$), 3.37 (dd, *J*=15.2, 10.8 Hz, 1H, $H8_a$), 3.98 (m, 1H, H9), 4.08 (m, 1H, H13), 4.44 (br dt, *J*=11.7, 4.8 Hz, 1H, $H15_a$), 4.88 (m, 1H, $H15_b$), 7.17 (br d, *J*=7.8 Hz, 1H, H6), 7.28 (dt, *J*=7.5, 1.2 Hz, 1H, H4), 7.35 (dt, *J*=7.5, 1.8 Hz, 1H, H5), 7.44 (dd, *J*=7.8, 1.8 Hz, 1H, H3); ^{13}C NMR (100 MHz) δ 32.9, 41.2, 45.8, 46.6, 62.1, 73.7, 73.8, 126.5, 127.3, 129.9, 131.4, 134.3, 134.8, 171.1, 205.9; HRMS (ESI) calcd for $C_{15}H_{16}O_4Na$ [M+Na^+]: 283.0946, found: 283.0950. Further elution gave the isomerised alkene **19** (1.3 mg, 22%).

*4.1.10. trans-Pyranone **21**.* To a stirred solution of enone **9** (12 mg, 0.047 mmol) in deuterochloroform (2 mL) was added Amberlyst-15 resin (6 mg,). The resulting suspension was heated under reflux for 22 h, then filtered and the solvent was removed under reduced pressure. Purification of the crude residue on silica gel using 30% EtOAc/petrol as eluent yielded an inseparable mixture of the major *trans*-pyranone **21** (6 mg, 50%) as a colourless crystalline solid as well as the diene product **22** (4 mg, 33%): mp 141–142 °C; IR ν_{max} (film) 3057 (C=C–H), 2987, 2966, 2927, 1721 (C=O), 1602 (Ar), 1266 (C–O), 1085 (C–O), 896 cm^{-1}; ^1H NMR (400 MHz) δ 1.61 (dd, J=15.2, 3.6 Hz, 1H, $H14_b$), 2.10 (m, 1H, $H14_a$), 2.23 (dd, J=18.0, 11.0 Hz, 1H, $H12_b$), 2.42 (dd, J=18.0, 3.2 Hz, 1H, $H12_a$), 2.48 (dd, J=13.6, 2.4 Hz, 1H, $H8_b$), 2.62 (d, J=8.4 Hz, 2H, H10), 3.79 (dd, J=13.6, 11.2 Hz, 1H, $H8_a$), 4.10 (m, 1H, H9), 4.23 (dd, J=11.6, 4.8 Hz, 1H, $H15_a$), 4.56 (dt, J=11.0, 3.2 Hz, 1H, H13), 5.11 (app dt, J=11.6, 3.6 Hz, 1H, $H15_b$), 7.22 (br d, J=7.6 Hz, 1H, H6), 7.31 (dt, J=7.2, 1.2 Hz, 1H, H4), 7.38 (dt, J=7.6, 1.2 Hz, 1H, H5), 7.53 (dd, J=7.2, 1.2 Hz, 1H, H3); ^{13}C NMR (100 MHz) δ 33.7, 39.0, 44.7, 46.9, 62.4, 68.4, 73.5, 126.8, 130.6, 135.2, 136.0, 171.0, 207.3; HRMS (ESI) calcd for $C_{15}H_{16}O_4Na$ [M+Na^+]: 283.0946, found: 283.0945.

*4.1.11. Diene **22**.* To a stirred solution of the isomerised alkene **19** (5 mg, 0.019 mmol) in deuterochloroform (0.5 mL) was added 3 beads of Amberlyst-15 resin. The resulting suspension was heated under reflux for 9 h, then filtered and the solvent was removed under reduced pressure. Purification of the crude residue on silica gel using 30% EtOAc/petrol as eluent yielded the diene **22** (4 mg, 86%) as a colourless thin film: IR ν_{max} (film) 3057 (C=C–H), 2986, 2963, 2928, 1712 (C=O), 1635 (C=C), 1600 (Ar), 1266 (C–O), 1127, 973, 905 cm^{-1}; ^1H NMR (300 MHz) δ 2.67 (app q, J=6.3 Hz, 2H, H14), 3.36 (dd, J=6.2, 1.2 Hz, 2H, H10), 4.46 (t, J=6.0 Hz, 2H, H15), 6.01 (dt, J=16.2, 6.2 Hz, 1H, H9), 6.30 (d, J=15.8 Hz, 1H, H12), 6.67 (dt, J=15.8, 7.5 Hz, 1H, H13), 6.72 (d, J=16.2 Hz, 1H, H8), 7.33 (t, J=7.5 Hz, 1H, H4), 7.38 (d, J=7.2 Hz, 1H, H6), 7.47 (t, J=8.4 Hz, 1H, H5), 7.78 (d, J=7.5 Hz, 1H, H3); ^{13}C NMR (100 MHz) δ 45.3, 53.4, 64.1, 124.8, 127.1, 127.5, 130.1, 130.5, 132.1, 134.8, 136.9, 137.6, 141.6, 168.8, 199.9; HRMS (ESI) calcd for $C_{15}H_{14}O_3Na$ [M+Na^+]: 265.0841, found: 265.0847.

*4.1.12. Alkene **24**.* A solution of vinyl stannane **15** (365 mg, 517 μmol) and benzyl bromide **7** (186 mg, 724 μmol) in NMP (3.8 mL) was freeze/thaw degassed twice. $Pd_2(dba)_3$ (22.5 mg, 26.1 μmol) and triphenylarsine (31.5 mg, 103 μmol) were then added and the reaction mixture was freeze/thaw degassed once more. After stirring overnight at 50 °C, the usual workup gave a residue, which was purified on silica gel with 10% EtOAc/petrol as eluent to yield the alkene **24** (288 mg, 92%) as a low melting point solid: IR ν_{max} (film) 3448 (O–H), 2945, 2893, 2866, 1741 (O=C–O), 1607 (Ar), 1584 (Ar), 1270 (C–O), 1080, 1048, 973 (C=C), 883 (Ar) cm^{-1}; ^1H NMR (300 MHz) δ 0.01 (s, 3H, SiMe), 0.04 (s, 3H, SiMe), 0.84 (s, 9H, $SiCMe_3$), 0.96 (s, 21H, $Si(CHMe_2)_3$), 1.57–1.73 (m, 2H, H7′), 1.67 (s, 6H, H9), 1.75–1.90 (m, 2H, H5′), 2.64 (br s, 1H, O*H*), 3.64 (m, 1H, H1′), 3.74–3.82 (br m, 3H, H1′, H8′), 3.98 (quint, J=5.7 Hz, 1H, H6′), 4.24 (app q, J=6.6 Hz, 1H, H4′), 5.41 (dd, J=15.3, 7.2 Hz, 1H, H3′), 5.76 (dt, J=15.3, 6.6 Hz, 1H, H2′), 6.81 (d, J=8.1 Hz, 1H, H8), 6.89 (d, J=7.8 Hz, 1H, H6), 7.39 (t, J=8.0 Hz, 1H, H7); ^{13}C NMR (75 MHz) δ −4.6, −4.5, 12.3, 17.8, 18.0, 18.04, 25.5, 25.7, 36.8, 38.3, 45.7, 59.9, 68.8, 71.1, 105.1, 111.8, 115.6, 125.0, 128.7, 134.9, 135.3, 145.0, 157.0, 160.2; HRMS (ESI) calcd for $C_{33}H_{58}O_6Si_2Na$ [M+Na^+]: 629.3670, found: 629.3674.

*4.1.13. Macrolactone **25**.* To a suspension of pentane-washed NaH (300 mg, 7.49 mmol, 60% dispersion in mineral oil) in THF (6.5 mL) was added dropwise the ester **24** (65 mg, 107 μmol) in THF (5 mL). After stirring 6 h at rt, when all the starting material has been consumed by TLC analysis, methyl iodide (133 μL, 2.14 mmol) was added dropwise. The resulting mixture was stirred for a further 17 h at rt then Et_2O was added and the reaction mixture was then cooled to 0 °C and acidified to pH 3 with cold 5% aqueous HCl. The usual workup produced a residue, which was purified on silica gel using 5% EtOAc/petrol as eluent to give the macrolactone **25** (47 mg, 80%) as a colourless crystalline solid: mp 69–70 °C; IR ν_{max} (film) 3054 (C=C–H), 2958, 2894, 2867, 1725 (O=C–O), 1598, 1585 (Ar), 1266 (C–O), 1079, 1070, 977, 884 cm^{-1}; ^1H NMR (400 MHz) δ −0.02 (s, 6H, $SiMe_2$), 0.85 (s, 9H, $SiCMe_3$), 1.03 (s, 21H, $Si(CHMe_2)_3$), 1.70–1.83 (m, 2H, H12, H14), 1.89–1.96 (m, 2H, H12, H14), 3.26 (d, J=15.0 Hz, 1H, H8), 3.53 (br m, 1H, H13), 3.63 (ddd, J=15.0, 8.4, 2.7 Hz, 1H, H8), 3.80 (s, 3H, OCH_3), 4.00–4.13 (m, 2H, H11, H15), 4.60 (ddd, J=11.1, 8.4, 2.7 Hz, 1H, H15), 5.34–5.37 (m, 2H, H9, H10), 6.81 (d, J=7.5 Hz, 1H, H4), 6.82 (d, J=8.4 Hz, 1H, H6), 7.27 (t, J=8.1 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ −4.5, −4.4, 12.2, 17.8, 18.0, 18.1, 25.8, 37.1, 37.3, 46.0, 56.1, 62.0, 66.0, 72.8, 109.9, 122.5, 128.3, 128.6, 130.3, 135.7, 138.6, 156.7, 168.2; HRMS (ESI) calcd for $C_{31}H_{54}O_5Si_2Na$ [M+Na^+]: 585.3407, found: 585.3401.

*4.1.14. Enone **23**.* To a stirred solution of lactone **25** (48 mg, 85.3 μmol) in THF (2 mL) was added TBAF (112 mg, 347 μmol) and the resulting solution was stirred for two days at rt. Ethyl acetate and water were then added and the organic extract was washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on silica gel using 80% EtOAc/petrol as eluent to give the diol (23 mg, 92%) as a colourless crystalline solid: mp 159–160 °C; IR ν_{max} (film) 3188 (O–H), 3056 (C=C–H), 2988, 2965, 2929, 2850, 1723 (O=C–O), 1585 (Ar), 1266 (C–O), 989, 896 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.68 (ddd, J=13.8, 11.4, 5.1 Hz, 1H, H12), 1.75–1.95 (m, 3H, H12, H14), 3.26 (dt, J=14.7, 2.7 Hz, 1H, H8), 3.45 (quint, J=5.7 Hz, 1H, H13), 3.59 (dd, J=14.7, 9.9 Hz, 1H, H8), 3.79 (s, 3H, OCH_3), 3.96–4.05 (m, 2H, H11, H15), 4.58 (ddd, J=11.4, 8.7, 2.7 Hz, 1H, H15), 5.29 (ddd, J=15.0, 8.7, 1.84 Hz, 1H, H10), 5.43 (ddd, J=15.0, 9.9, 2.7 Hz, 1H, H9), 6.84 (d, J=7.8 Hz, 1H, H4), 6.94 (d, J=8.1 Hz, 1H, H6), 7.31 (t, J=8.1 Hz, 1H, H5); ^{13}C NMR (100 MHz, CD_3OD) δ 37.7, 38.1, 45.2, 56.4, 62.9, 65.78, 73.4, 111.0, 123.4, 125.4, 131.5, 131.9, 135.6, 139.6, 158.2, 169.8; HRMS (ESI) calcd for $C_{16}H_{20}O_5Na$ [M+Na^+]: 315.1208, found: 315.1215.

To a stirred solution of above diol (13 mg, 44.5 μmol) in dichloromethane (2.5 mL) was added MnO_2 (78 mg, 0.89 mmol) and the resulting suspension was stirred overnight at rt. The mixture was then diluted with dichloromethane and filtered through Celite. Concentration of the filtrate under reduced pressure and purification of the crude residue by flash chromatography using 60% ethyl EtOAc/petrol as eluent afforded the enone **23** (7 mg, 71% based on recovered starting material (3 mg)) as a colourless thin film: IR ν_{max} (film) 3441 (O–H), 2962, 2842, 1724 (C=O), 1631 (C=C), 1597, 1583 (Ar), 1272, 1085, 1069 (C–O), 986 cm^{-1}; ^1H NMR (300 MHz) δ 1.96–2.02 (m, 2H, H14), 2.57 (d, J=6.9 Hz, 1H, O*H*), 2.72 (dd, J=12.9, 8.1 Hz, 1H, H12), 2.97 (dd, J=12.9, 3.9 Hz, 1H, H12), 3.56 (ddd, J=17.7, 5.0, 1.8 Hz, 1H, H8), 3.82 (dd, J=17.7, 7.1 Hz, 1H, H8), 3.84 (s, 3H, OCH_3), 4.15–4.23 (m, 2H, H13, H15), 4.64 (ddd, J=12.0, 6.3, 3.6 Hz, 1H, H15), 6.16 (br d, J=15.9 Hz, 1H, H10), 6.75 (ddd, J=15.9, 7.1, 5.0 Hz, 1H, H9), 6.83 (d, J=7.5 Hz, 1H, H4), 6.89 (d, J=8.4 Hz, 1H, H6), 7.32 (t, J=8.1 Hz, 1H, H5); ^{13}C NMR (75 MHz) δ 34.8, 36.8, 46.4, 56.1, 62.4, 68.5, 110.2, 122.9, 124.1, 130.9, 133.4, 136.6, 144.6, 157.0, 168.4, 201.3; HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ [M+Na^+]: 313.1052, found: 313.1058.

*4.1.15. trans-Pyranone **26**.* To a stirred solution of enone **23** (6 mg, 20.7 μmol) in deuterochloroform (2 mL) was added Amberlyst-15 resin (10 mg). The resulting suspension was heated under reflux for 25 h, then filtered and the solvent concentrated under reduced pressure. Purification of the crude residue on silica gel using 30% EtOAc/petrol as eluent yielded an inseparable mixture of the major *trans*-pyranone **26** (5 mg, 83%) as a colourless crystalline solid: mp

186–187 °C; IR ν_{max} (film) 3056 (C=C–H), 2988, 2929, 2856, 1720 (C=O), 1641, 1600, 1583 (Ar), 1266, 1104 (C–O) cm^{-1}; ^1H NMR (400 MHz) δ 1.65 (br d, J=16.0 Hz, 1H, $H14_b$), 2.04 (br m, 1H, $H14_a$), 2.24 (dd, J=17.6, 10.4 Hz, 1H, $H12_b$), 2.46 (dd, J=17.6, 3.6 Hz, 1H, $H12_a$), 2.51 (br d, J=13.6 Hz, 1H, $H8_b$), 2.58 (dd, J=15.6, 9.2 Hz, 1H, H10), 2.66 (dd, J=15.2, 6.4 Hz, 1H, H10), 3.48 (dd, J=13.6, 11.6 Hz, 1H, $H8_a$), 3.84 (s, 3H, OCH_3), 4.04 (dd, J=11.2, 4.8 Hz, 1H, $H15_a$), 4.24 (m, 1H, H9), 4.49 (dt, J=10.0, 3.2 Hz, 1H, H13), 5.44 (m, 1H, $H15_b$), 6.82 (d, J=7.6 Hz, 1H, H4), 6.86 (d, J=8.4 Hz, 1H, H6), 7.30 (t, J=8.0 Hz, 1H, H5); ^{13}C NMR (75 MHz) δ 34.7, 39.0, 45.1, 47.0, 56.0, 62.2, 66.4, 73.8, 109.9, 122.7, 130.6, 137.3, 155.9, 170.1, 200.3; HRMS (ESI) calcd for $C_{16}H_{18}O_5Na$ [M+Na^+]: 313.1052, found: 313.1059.

*4.1.16. Alcohols rac-**32** and rac-**33**.* To a stirred solution of alcohol *rac*-**14** (1.50 g, 3.08 mmol) in CH_2Cl_2 (43 mL) was added pyridine (1.3 mL, 15.4 mmol) and Dess–Martin periodinane (2.61 g, 6.16 mmol) and the reaction mixture was stirred for 1 h at rt. 0.5 M $Na_2S_2O_3$ (70 mL), saturated $NaHCO_3$ (70 mL) and Et_2O (140 mL) were added and the resulting mixture was stirred vigorously until two clear layers formed. The usual pyridine workup produced the crude aldehyde, (1.40 g) as a pale yellow oil, which was used in the next step without purification. A solution of 3-bromo-1-propene (2.22 g, 18.5 mmol) in Et_2O (75 mL) was added dropwise to flame dried magnesium (453 mg, 18.8 mmol) and a crystal of iodine. After stirring for 30 min at rt, a solution of the crude aldehyde (1.40 g, 2.89 mmol) in Et_2O (30 mL) was added dropwise to the resultant Grignard reagent over a period of 5 min at 0 °C. After stirring at 0 °C for further 20 min, saturated NH_4Cl was added slowly and the aqueous phase was extracted. The usual workup and the purification of the crude product by flash chromatography using 2.5% EtOAc/petrol as eluent yielded an inseparable racemic mixture of the alcohols (1.11 g, 73%) as a colourless oil.

To a stirred solution of the racemic alcohols (1.11 g, 2.11 mmol) in methanol (3 mL) was added K_2CO_3 (276 mg, 1.97 mmol). After stirring for 2 h at rt, the solvent was removed and the usual workup followed by purification of the crude product by flash chromatography using 2.5–5% EtOAc/petrol as eluent gave the alcohol *rac*-**32** (374 mg, 39%) as a colourless oil: ^1H NMR (400 MHz) δ 0.11 (s, 6H, $SiMe_2$), 0.89 (s, 9H, $SiCMe_3$), 1.01–1.16 (m, 21H, $Si(CHMe_2)_3$), 1.59 (ddd, J=14.0, 7.2, 2.4 Hz, 1H, H5), 1.79 (ddd, J=14.0, 6.0, 2.4 Hz, 1H, H5), 1.86–1.99 (m, 2H, H7), 2.18–2.26 (m, 2H, H3), 2.43 (d, J=2.0 Hz, 1H, H10), 2.63 (br s, 1H, O*H*), 3.80 (m, 1H, H4), 4.17 (app quint, J=6.4 Hz, 1H, H6), 4.58 (dt, J=6.8, 2.0 Hz, 1H, H8), 5.10 (d, J=10.4 Hz, 1H, H1), 5.11 (dd, J=17.2, 1.2 Hz, 1H, H1), 5.81 (dddd, J=17.2, 10.4, 7.2, 7.2 Hz, 1H, H2); ^{13}C NMR (100 MHz) δ −4.5, −4.3, 12.2, 17.8, 18.0, 18.03, 25.8, 42.4, 43.6, 46.5, 60.6, 69.1, 69.2, 73.0, 85.1, 117.8, 134.7; HRMS (ESI) calcd for $C_{25}H_{50}O_3Si_2Na$ [M+Na^+]: 477.3196, found: 477.3200.

Further elution afforded a fraction of mixed alcohols *rac*-**32** and *rac*-**33** (25 mg, 3%). Further elution then alcohols *rac*-**33** (487 mg, 51%) as a pale yellow oil: ^1H NMR (400 MHz) δ 0.09 (s, 3H, SiMe), 0.11 (s, 3H, SiMe), 0.87 (s, 9H, $SiCMe_3$), 1.01–1.15 (m, 21H, $Si(CHMe_2)_3$), 1.62 (ddd, J=14.4, 3.9, 3.3 Hz, 1H, H5), 1.71 (ddd, J=14.4, 9.6, 4.5 Hz, 1H, H5), 1.89 (ddd, J=13.5, 8.4, 4.8 Hz, 1H, H7), 2.04 (ddd, J=13.5, 8.1, 5.4 Hz, 1H, H7), 2.12–2.27 (m, 2H, H3), 2.43 (d, J=2.1 Hz, 1H, H10), 3.34 (br s, 1H, O*H*), 4.00 (m, 1H, H4), 4.24 (m, 1H, H6), 4.53 (ddd, J=8.4, 5.4, 2.1 Hz, 1H, H8), 5.06 (d, J=10.2 Hz, 1H, H1), 5.07 (d, J=17.1 Hz, 1H, H1), 5.81 (dddd, J=17.1, 10.2, 7.2, 6.9 Hz, 1H, H2); ^{13}C NMR (100 MHz) δ −4.5, −4.6, 12.1, 17.8, 17.9, 18.0, 25.7, 41.9, 42.3, 45.0, 60.8, 67.9, 68.8, 73.2, 85.1, 117.3, 134.8; HRMS (ESI) calcd for $C_{25}H_{50}O_3Si_2Na$ [M+Na^+]: 477.3196, found: 477.3198.

*4.1.17. Alcohols rac-**28** and rac-**29**.* The racemic alcohols *rac*-**28** and *rac*-**29** were prepared from alcohol *rac*-**13** (4.0 g, 8.25 mmol) using the procedure described above. Purification by flash chromatography with 5% EtOAc/petrol as eluent afforded the alcohol *rac*-**28** (1.34 g, 31%) as a colourless oil: IR ν_{max} (film) 3487 (O–H), 2959, 2947, 2895, 2171 (C≡C), 1642 (C=C), 1265, 1252 (C–O), 1089, 1063, 1000, 843 cm^{-1}; ^1H NMR (400 MHz) δ 0.117 (s, 3H, SiMe), 0.12 (s, 3H, SiMe), 0.15 (s, 9H, $SiMe_3$), 0.90 (s, 9H, $SiCMe_3$), 1.06–1.09 (m, 18H, $Si(CHMe_2)_3$), 1.11–1.19 (m, 3H, $Si(CHMe_2)_3$), 1.64 (ddd, J=14.4, 4.4, 2.8 Hz, 1H, H5), 1.71 (ddd, J=14.4, 9.6, 4.0 Hz, 1H, H5), 1.99 (ddd, J=13.6, 8.0, 4.8 Hz, 1H, H7), 2.06 (ddd, J=13.6, 8.4, 6.0 Hz, 1H, H7), 2.18 (ddd, J=13.6, 7.2, 6.4 Hz, 1H, H3), 2.26 (ddd, J=13.6, 7.2, 6.8 Hz, 1H, H3), 3.48 (br s, 1H, O*H*), 4.04 (dddd, J=9.6, 6.8, 6.4, 2.8 Hz, 1H, H4), 4.26 (m, 1H, H6), 4.37 (dd, J=8.4, 6.0 Hz, 1H, H8), 5.08 (dd, J=10.0, 2.0 Hz, 1H, H1), 5.10 (dd, J=17.2, 2.0 Hz, 1H, H1), 5.83 (dddd, J=17.2, 10.0, 7.2, 7.2 Hz, 1H, H2); ^{13}C NMR (100 MHz) δ −4.8, −4.5, −0.3, 12.4, 17.9, 18.0, 25.8, 40.7, 42.3, 44.7, 60.5, 67.9, 68.8, 89.7, 107.0, 117.3, 135.0; HRMS (ESI) calcd for $C_{28}H_{58}O_3Si_3Na$ [M+Na^+]: 549.3591, found: 549.3590.

Further elution gave mixed fraction (240 mg, 6%) followed by pure alcohol *rac*-**29** (2.32 g, 54%) as a colourless oil: ^1H NMR (400 MHz) δ 0.13 (s, 3H, SiMe), 0.14 (s, 3H, SiMe), 0.15 (s, 9H, $SiMe_3$), 0.90 (s, 9H, $SiCMe_3$), 1.06–1.09 (m, 18H, $Si(CHMe_2)_3$), 1.10–1.19 (m, 3H, $Si(CHMe_2)_3$), 1.57 (ddd, J=14.0, 8.8, 7.0 Hz, 1H, H5), 1.78 (ddd, J=14.0, 3.6, 3.2 Hz, 1H, H5), 1.89 (ddd, J=13.2, 8.4, 5.4 Hz, 1H, H7), 1.99 (ddd, J=13.2, 8.6, 4.4 Hz, 1H, H7), 2.20–2.28 (m, 2H, H3), 2.98 (s, 1H, O*H*), 3.84 (br m, 1H, H4), 4.10 (m, 1H, H6), 4.43 (dd, J=8.6, 5.4 Hz, 1H, H8), 5.09–5.14 (m, 2H, H1), 5.84 (dddd, J=17.2, 10.4, 7.2, 6.8 Hz, 1H, H2); ^{13}C NMR (100 MHz) δ −4.6, −3.9, −0.3, 12.4, 17.9, 18.1, 25.9, 42.0, 42.9, 47.0, 60.4, 69.8, 70.1, 89.6, 107.2, 117.5, 134.9; HRMS (ESI) calcd for $C_{28}H_{58}O_3Si_3Na$ [M+Na^+]: 549.3591, found: 549.3574.

*4.1.18. Alkyne rac-**35**.* To a stirred solution of the racemic TMS acetylene *rac*-**29** (1.04 g, 1.97 mmol) in methanol (3 mL) was added K_2CO_3 (276 mg, 1.97 mmol). After stirring for 2 h at rt, the solvent was removed and the usual workup followed by purification of the crude product by flash chromatography using 5% EtOAc/petrol as eluent gave the alkyne *rac*-**35** (716 mg, 80%) as a colourless oil: IR ν_{max} (film) 3480, 3304, 3054, 2947, 2894, 2868, 2306, 1642, 1266, 1060, 1000, 838 cm^{-1}; ^1H NMR (400 MHz) δ 0.11 (s, 3H, SiMe), 0.12 (s, 3H, SiMe), 0.90 (s, 9H, $SiCMe_3$), 1.07–1.09 (m, 18H, $Si(CHMe_2)_3$), 1.10–1.18 (m, 3H, $Si(CHMe_2)_3$), 1.64–1.74 (m, 2H, H5), 2.03 (ddd, J=13.2, 8.0, 5.2 Hz, 1H, H7), 2.08 (ddd, J=13.2, 8.4, 6.0 Hz, 1H, H7), 2.18 (ddd, J=14.0, 7.2, 6.4 Hz, 1H, H3), 2.27 (ddd, J=14.0, 7.2, 6.8 Hz, 1H, H3), 2.43 (d, J=2.2 Hz, 1H, H10), 3.43 (s, 1H, O*H*), 4.03 (br m, 1H, H4), 4.27 (m, 1H, H6), 4.42 (ddd, J=8.0, 6.0, 2.2 Hz, 1H, H8), 5.08 (d, J=10.0 Hz, 1H, H1), 5.10 (dd, J=17.2, 1.6 Hz, 1H, H1), 5.83 (dddd, J=17.2, 10.0, 7.2, 6.8 Hz, 1H, H2); ^{13}C NMR (100 MHz) δ −4.8, −4.6, 12.3, 17.9, 18.0, 18.1, 25.8, 40.7, 42.3, 44.7, 60.0, 67.9, 68.7, 73.2, 85.0, 117.4, 134.9; HRMS (ESI) calcd for $C_{25}H_{50}O_3Si_2Na$ [M+Na^+]: 477.3196, found: 477.3174.

*4.1.19. Alkyne rac-**34**.* Deprotection of the racemic TMS acetylene *rac*-**28** (1.5 g, 2.85 mmol) was performed in the same manner as described above. Purification by flash chromatography with 2.5% EtOAc/petrol as eluent afforded the alkyne *rac*-**34** (1.20 g, 93%) as a colourless oil: IR ν_{max} (film) 3472, 3312, 3078, 2947, 2894, 2868, 2113, 1642, 1257, 1094, 999, 837 cm^{-1}; ^1H NMR (400 MHz) δ 0.13 (s, 6H, $SiMe_2$), 0.90 (s, 9H, $SiCMe_3$), 1.07–1.09 (m, 18H, $Si(CHMe_2)_3$), 1.10–1.18 (m, 3H, $Si(CHMe_2)_3$), 1.56 (ddd, J=14.2, 8.8, 8.8 Hz, 1H, H5), 1.77 (ddd, J=14.2, 4.0, 3.2 Hz, 1H, H5), 1.92 (ddd, J=13.2, 8.4, 5.8 Hz, 1H, H7), 2.03 (ddd, J=13.2, 8.2, 4.4 Hz, 1H, H7), 2.17–2.29 (m, 2H, H3), 2.43 (d, J=2.0 Hz, 1H, H10), 2.93 (s, 1H, O*H*), 3.85 (br m, 1H, H4), 4.11 (m, 1H, H6), 4.47 (ddd, J=8.2, 5.8, 2.0, 1H, H8), 5.10 (d, J=10.4 Hz, 1H, H1), 5.11 (d, J=16.8 Hz, 1H, H1), 5.84 (dddd, J=16.8, 10.4, 7.2, 7.2 Hz, 1H, H2); ^{13}C NMR (100 MHz) δ −4.6, −4.0, 12.3, 17.9, 18.0, 18.1, 25.8, 42.0, 42.9, 47.1, 59.9, 69.7, 69.9, 73.1, 85.1, 117.5, 134.8; HRMS (ESI) calcd for $C_{25}H_{50}O_3Si_2Na$ [M+Na^+]: 477.3196, found: 477.3195.

*4.1.20. Stannane rac-**36**.* To a stirred solution of the racemic alkyne *rac*-**34** (1.59 g, 3.50 mmol) in CH_2Cl_2 (64 mL) at 0 °C was added $Pd(PPh_3)_2Cl_2$ (398 mg, 557 μmol). After stirring for 10 min at 0 °C, Bu_3SnH (1.55 mL, 5.25 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and then filtered through Celite and the solvent removed under reduced pressure. Purification of the residue by flash chromatography using 1% NEt_3/1–5% EtOAc/petrol as eluent afforded the vinyl stannane *rac*-**36** (1.34 g, 93%) as a colourless oil: IR ν_{max} (film) 3506, 3051, 2956, 2930, 1641, 1265, 1065, 995, 837 cm^{-1}; ^1H NMR (400 MHz) δ 0.07 (s, 6H, $SiMe_2$), 0.80–0.98 (m, 15H, Sn*Bu*$_3$), 0.88 (s, 9H, $SiCMe_3$), 1.02–1.07 (m, 21H, Si(C*H*Me_2)$_3$), 1.29 (sext, *J*=7.2 Hz, 6H, Sn*Bu*$_3$), 1.43–1.56 (m, 6H, Sn*Bu*$_3$), 1.61–1.64 (m, 2H, H5), 1.74 (ddd, *J*=13.6, 9.6, 4.0 Hz, 1H, H7), 2.05 (ddd, *J*=13.6, 10.4, 4.4 Hz, 1H, H7), 2.15 (ddd, *J*=13.6, 6.8, 6.8 Hz, 1H, H3), 2.28 (ddd, *J*=13.6, 7.2, 6.8 Hz, 1H, H3), 3.67 (s, 1H, O*H*), 3.95–4.00 (m, 2H, 4, 6), 4.04 (m, 1H, H8), 5.09 (d, *J*=10.0 Hz, 1H, H1), 5.10 (d, *J*=17.2 Hz, 1H, H1), 5.83 (dddd, *J*=17.2, 10.0, 7.2, 6.8 Hz, 1H, H2), 5.88 (dd, *J*=19.2, 6.8 Hz, 1H, H9), 6.00 (d, *J*=19.2 Hz, 1H, H10); ^{13}C NMR (100 MHz) δ −4.9, −4.5, 9.4, 12.4, 13.7, 17.9, 18.1, 18.14, 25.8, 27.3, 29.1, 39.9, 42.3, 44.1, 67.8, 69.3, 75.0, 117.2, 129.1, 135.0, 151.0; HRMS (ESI) calcd for $C_{37}H_{78}O_3Si_2SnNa$ [M+Na^+]: 767.4409, found: 767.4409.

*4.1.21. Stannane rac-**37**.* The hydrostannylation of the racemic alkyne *rac*-**35** (2.44 g, 5.37 mmol) was performed in the same manner described above. Purification by flash chromatography with 1% NEt_3/1–5% EtOAc/petrol as eluent gave the vinyl stannane *rac*-**37** (3.70 g, 92%) as a colourless oil: IR ν_{max} (film) 3507, 3078, 2958, 2930, 2868, 1642, 1255, 1062, 994, 837 cm^{-1}; ^1H NMR (400 MHz) δ 0.09 (s, 3H, SiMe), 0.10 (s, 3H, SiMe), 0.80–0.97 (m, 15H, Sn*Bu*$_3$), 0.89 (s, 9H, $SiCMe_3$), 1.04–1.05 (m, 21H, Si(C*H*Me_2)$_3$), 1.30 (sext, *J*=7.2 Hz, 6H, Sn*Bu*$_3$), 1.42–1.55 (m, 6H, Sn*Bu*$_3$), 1.72–1.86 (m, 4H, H5, H7), 2.21 (dd, *J*=6.8, 6.4 Hz, 2H, H3), 3.35 (s, 1H, O*H*), 3.78–3.84 (m, 2H, H4, H6), 4.03 (m, 1H, H8), 5.08–5.12 (m, 2H, H1), 5.85 (dddd, *J*=16.8, 10.4, 7.2, 6.8 Hz, 1H, H2), 5.87 (dd, *J*=19.2, 6.6 Hz, 1H, H9), 5.97 (d, *J*=19.2 Hz, 1H, H10); ^{13}C NMR (100 MHz) δ −4.6, −3.8, 9.4, 12.3, 13.7, 17.8, 18.0, 18.1, 25.8, 27.3, 29.1, 41.8, 42.5, 47.1, 70.4, 71.1, 75.1, 117.3, 128.9, 134.9, 151.1; HRMS (ESI) calcd for $C_{37}H_{78}O_3Si_2SnNa$ [M+Na^+]: 767.4409, found: 767.4407.

*4.1.22. Stannane rac-**38**.* The hydrostannylation of the alkyne *rac*-**32** (374 mg, 0.822 μmol) was performed in the same manner described above. Purification by flash chromatography with 1% NEt_3/1–5% EtOAc/petrol as eluent gave the vinyl stannane *rac*-**38** (435 mg, 71%) as a colourless oil: ^1H NMR (400 MHz) δ 0.105 (s, 3H, SiMe), 0.11 (s, 3H, SiMe), 0.80–0.99 (m, 15H, Sn*Bu*$_3$), 0.89 (s, 9H, $SiCMe_3$), 1.04–1.05 (m, 21H, $Si(CHMe_2)_3$), 1.30 (sext, *J*=7.2 Hz, 6H, Sn*Bu*$_3$), 1.41–1.54 (m, 6H, Sn*Bu*$_3$), 1.55–1.69 (m, 2H, H5), 1.79–1.93 (m, 2H, H7), 2.19–2.24 (m, 2H, H3), 3.27 (d, *J*=0.9 Hz, 1H, O*H*), 3.79 (m, 1H, H4), 4.09 (m, 1H, H6), 4.26 (m, 1H, H8), 5.06–5.13 (m, 2H, H1), 5.82 (dddd, *J*=17.1, 10.2, 7.2, 7.2 Hz, 1H, H2), 5.89 (dd, *J*=19.2, 6.3 Hz, 1H, H9), 6.07 (d, *J*=19.2 Hz, 1H, H10); ^{13}C NMR (75 MHz) δ −4.5, −3.9, 9.4, 12.5, 13.7, 17.8, 18.2, 25.8, 27.3, 29.1, 42.2, 43.0, 46.9, 70.3, 70.7, 74.5, 117.3, 127.8, 134.9, 151.3; HRMS (ESI) calcd for $C_{37}H_{78}O_3Si_2SnNa$ [M+Nai$^+$]: 767.4409, found: 767.4416.

*4.1.23. Stannane rac-**39**.* The hydrostannylation of the alkyne *rac*-**33** (466 mg, 1.02 mmol) was performed in the same manner described above. Purification by flash chromatography with 1% NEt_3/1–5% EtOAc/petrol as eluent gave the vinyl stannane *rac*-**39** (507 mg, 67%) as a colourless oil: ^1H NMR (400 MHz) δ 0.08 (s, 3H, SiMe), 0.10 (s, 3H, SiMe), 0.79–0.98 (m, 15H, Sn*Bu*$_3$), 0.89 (s, 9H, $SiCMe_3$), 1.04–1.05 (m, 21H, Si(C*H*Me_2)$_3$), 1.30 (sext, *J*=7.2 Hz, 6H, Sn*Bu*$_3$), 1.42–1.54 (m, 6H, Sn*Bu*$_3$), 1.67–1.71 (m, 2H, H5), 1.76 (m, 1H, H7), 1.92 (ddd, *J*=13.8, 6.6, 6.3 Hz, 1H, H7), 2.12–2.30 (m, 2H, H3), 3.59 (d, *J*=0.9 Hz, 1H, O*H*), 4.04 (m, 1H, H4), 4.11–4.23 (m, 2H, H6, H8), 5.06–5.12 (m, 2H, H1), 5.84 (dddd, *J*=17.1, 10.5, 6.9, 6.9 Hz, 1H, H2), 5.92 (dd, *J*=18.9, 6.3 Hz, 1H, H9), 6.07 (d, *J*=18.9 Hz, 1H, H10); ^{13}C NMR (75 MHz) δ −4.6, −4.5, 9.4, 12.5, 13.7, 17.9, 18.1, 25.8, 27.3, 29.1, 40.6, 42.3, 44.5, 67.9, 69.2, 74.7, 117.1, 128.3, 135.0, 151.3; HRMS (ESI) calcd for $C_{37}H_{78}O_3Si_2SnNa$ [M+Na^+]: 767.4409, found: 767.4413.

*4.1.24. Alkene rac-**40**.* A solution of the racemic vinyl stannane *rac*-**38** (200 mg, 268 μmol) and benzyl bromide **7** (80.6 mg, 347 μmol) in NMP (880 μL) was freeze/thaw degassed twice. $Pd_2(dba)_3$ (11.7 mg, 13.6 μmol) and tris-2-furyl phosphine (12.2 mg, 11.7 μmol) were then added and the reaction mixture was freeze/thaw degassed once more. After stirring for 30 h at 50 °C, the usual workup gave a residue, which was purified on silica gel with 5% EtOAc/petrol as eluent to yield the alkene *rac*-**40** (143 mg, 82%) as a colourless oil: ^1H NMR (400 MHz) δ 0.04 (s, 3H, SiMe), 0.07 (s, 3H, SiMe), 0.87 (s, 9H, $SiCMe_3$), 0.98 (s, 21H, $Si(CHMe_2)_3$), 1.63–1.79 (m, 3H, H5′, H7′), 1.69 (s, 6H, H9), 1.89 (m, 1H, H5′), 2.10–2.28 (m, 2H, H9′), 3.49 (d, *J*=1.5 Hz, 1H, O*H*), 3.76–3.91 (m, 2H, H1′), 3.99 (br m, 1H, H8′), 4.12 (br m, 1H, H6′), 4.28 (app q, *J*=6.9 Hz, 1H, H4′), 5.05–5.10 (m, 2H, H11′), 5.45 (dd, *J*=15.6, 7.5 Hz, 1H, H3′), 5.74–5.89 (m, 2H, H2′, H10′), 6.83 (d, *J*=8.1 Hz, 1H, H8), 6.91 (d, *J*=7.8 Hz, 1H, H6), 7.41 (dd, *J*=8.1, 7.8 Hz, 1H, H7); ^{13}C NMR (75 MHz) δ −4.5, −4.1, 12.4, 17.8, 18.1, 18.12, 25.6, 25.8, 36.8, 42.2, 43.2, 47.2, 70.0, 70.1, 71.1, 105.1, 111.9, 115.6, 117.3, 125.1, 128.5, 135.0, 135.3, 145.1, 157.1, 160.2; HRMS (ESI) calcd for $C_{35}H_{62}O_6Si_2Na$ [M+Na^+]: 669.3983, found: 669.3970.

*4.1.25. Macrolactone rac-**41**.* To a suspension of pentane-washed NaH (478 mg, 12.5 mmol, 60% dispersion in mineral oil) in THF (10.3 mL) was added dropwise a solution of the alkene *rac*-**40** (110 mg, 170 μmol) in THF (8 mL) and the resulting mixture was stirred for 4 h at rt. Et_2O was then added and the reaction mixture was cooled to 0 °C and acidified to pH 3 with cold 5% aqueous HCl. The usual workup produced a residue, which was purified on silica gel using 2.5% EtOAc/petrol as eluent to give the macrolactone *rac*-**41** (80 mg, 80%) as a colourless oil: ^1H NMR (300 MHz) δ 0.01 (s, 3H, SiMe), 0.04 (s, 3H, SiMe), 0.88 (s, 9H, $SiCMe_3$), 1.02 (s, 21H, Si(C*H*Me_2)$_3$), 1.65–1.80 (m, 2H, H12, H14), 1.96 (dd, *J*=13.2, 6.0 Hz, 1H, H14), 2.08 (dd, *J*=15.0, 11.1 Hz, 1H, H12), 2.41 (app t, *J*=6.6 Hz, 2H, H1′), 3.36 (dd, *J*=8.7, 8.1 Hz, 1H, H13), 3.48 (m, 1H, H8), 3.92 (dd, *J*=16.8, 5.1 Hz, 1H, H8), 4.17 (m, 1H, H11), 5.07–5.12 (m, 2H, H3′), 5.26–5.39 (m, 3H, H9, H10, H15), 5.76 (m, 1H, H2′), 6.75 (d, *J*=7.2 Hz, 1H, H4), 6.92 (d, *J*=8.4 Hz, 1H, H6), 7.32 (t, *J*=7.8 Hz, 1H, H5), 11.48 (br s, 1H, ArO*H*); ^{13}C NMR (100 MHz) δ −4.7, −4.3, 12.2, 17.8, 18.0, 18.02, 25.8, 38.7, 39.1, 43.5, 46.4, 64.2, 73.3, 74.6, 112.2, 116.9, 118.7, 123.2, 130.7, 132.5, 133.6, 134.3, 143.5, 163.5, 170.7; HRMS (ESI) calcd for $C_{33}H_{56}O_5Si_2Na$ [M+Na^+]: 611.3564, found: 611.3567.

*4.1.26. Macrolactone triol rac-**42**.* To a stirred solution of lactone *rac*-**41** (40 mg, 68 μmol) in THF (1.1 mL) was added TBAF (89 mg, 0.27 mmol) and the resulting solution was stirred for two days at rt. Ethyl acetate and water were then added and the organic extract was washed with water, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified on silica gel using 30% EtOAc/CH_2Cl_2 as eluent to give the triol *rac*-**42** (20.5 mg, 95%) as a colourless crystalline solid: IR ν_{max} (film) 3584, 3491, 3055, 2985, 2927, 2856, 1730, 1265, 979 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.50–1.62 (m, 2H, H14), 1.89 (ddd, *J*=13.0, 5.4, 2.2 Hz, 1H, H12), 2.02 (m, 1H, H12), 2.35 (dd, *J*=6.4, 6.4 Hz, 2H, H1′), 3.29 (m, 1H, H13), 3.41 (m, 1H, H8), 3.67 (dd, *J*=16.4, 6.0 Hz, 1H, H8), 4.01 (m, 1H, H11), 4.98–5.04 (m, 2H, H3′), 5.21 (dd, *J*=15.6, 8.4 Hz, 1H, H10), 5.28–5.37 (m, 2H, H9, H15), 5.74 (dddd, *J*=17.2, 10.4, 7.2, 6.8 Hz, 1H, H2′), 6.36 (d, *J*=7.6 Hz, 1H, H4), 6.50 (d, *J*=8.4 Hz, 1H, H6), 6.91 (t, *J*=8.0 Hz, 1H, H5), 10.59 (br s, 1H, ArO*H*); ^{13}C NMR (100 MHz, acetone-d_6) δ 38.1, 40.6, 44.2, 47.5, 48.5, 68.2, 72.9, 76.3, 116.6, 118.5,

119.2, 123.5, 131.6, 133.5, 135.1, 135.5, 142.4, 160.1, 171.3; HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ [M+Na$^+$]: 341.1365, found: 341.1370.

*4.1.27. Alkene rac-**43**.* Stille coupling between the vinyl stannane *rac*-**39** (380 mg, 510 μmol) and the benzyl bromide **7** (153 mg, 661 μmol) was performed in the same manner as described above. Purification by flash chromatography with 5–10% EtOAc/petrol as eluent afforded the alkene *rac*-**43** (200 mg, 61%) as a colourless oil: ^{1}H NMR (400 MHz) δ 0.05 (s, 3H, SiMe), 0.08 (s, 3H, SiMe), 0.87 (s, 9H, SiCMe$_3$), 0.98 (s, 21H, Si(C*H*Me$_2$)$_3$), 1.43–1.62 (m, 2H, H7′), 1.69 (s, 6H, H9), 1.75–1.84 (m, 2H, H5′), 2.12–2.30 (m, 2H, H9′), 3.25 (br s, 1H, O*H*), 3.74 (m, 1H, H8′), 3.81–3.84 (m, 2H, H1′), 4.03 (m, 1H, H6′), 4.28 (app q, *J*=7.5 Hz, 1H, H4′), 5.06 (dd, *J*=10.2, 1.8 Hz, 1H, H11′), 5.08 (dd, *J*=17.4, 1.8 Hz, 1H, H11′), 5.43 (dd, *J*=15.6, 7.5 Hz, 1H, H3′), 5.73–5.87 (m, 2H, H2′, H10′), 6.83 (d, *J*=8.1 Hz, 1H, H8), 6.91 (d, *J*=7.8 Hz, 1H, H6), 7.41 (dd, *J*=8.1, 7.8 Hz, 1H, H7); ^{13}C NMR (75 MHz) δ −4.5, −4.1, 12.4, 17.8, 18.1, 18.12, 25.6, 25.8, 36.8, 42.2, 43.2, 47.2, 70.0, 70.1, 71.1, 105.1, 111.9, 115.6, 117.3, 125.1, 128.5, 135.0, 135.3, 145.1, 157.1, 160.2; HRMS (ESI) calcd for $C_{35}H_{62}O_6Si_2Na$ [M+Na$^+$]: 669.3983, found: 669.3991.

*4.1.28. Alkene rac-**44**.* Stille coupling between the racemic vinyl stannane **37** (2.00 g, 2.68 mmol) and the benzyl bromide **7** (938 mg, 4.00 mmol) was performed in the same manner as described above. Purification by flash chromatography with 5–10% EtOAc/petrol as eluent afforded the ester *rac*-**44** (1.47 g, 85%) as a colourless oil: IR ν_{max} (film) 3504, 3055, 2946, 2866, 1735, 1607, 1266, 1079, 976, 884, 838 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.07 (s, 6H, Si(Me)$_2$), 0.88 (s, 9H, SiCMe$_3$), 1.00 (s, 21H, Si(CHMe$_2$)$_3$), 1.45 (ddd, *J*=14.0, 9.2, 8.8 Hz, 1H, H7′), 1.68 (ddd, *J*=14.0, 3.2, 2.8 Hz, 1H, H7′), 1.69 (s, 3H, H9), 1.71 (s, 3H, H9), 1.72 (ddd, *J*=13.2, 8.6, 4.0 Hz, 1H, H5′), 1.81 (ddd, *J*=13.2, 9.6, 5.2 Hz, 1H, H5′), 2.16 (dd, *J*=6.8, 6.4 Hz, 2H, H9′), 3.20 (s, 1H, O*H*), 3.73–3.79 (m, 2H, H6′, H8′), 3.80–3.89 (m, 2H, H1′), 4.11 (ddd, *J*=8.6, 8.2, 5.2 Hz, 1H, H4′), 5.05–5.09 (m, 2H, H11′), 5.41 (dd, *J*=15.6, 8.2, 1H, H3′), 5.70–5.84 (m, 2H, H2′, H10′), 6.83 (d, *J*=8.0 Hz, 1H, H8), 6.91 (d, *J*=7.6 Hz, 1H, H6), 7.41 (t, *J*=7.8 Hz, 1H, H7); ^{13}C NMR (100 MHz) δ −4.6, −3.9, 12.4, 17.9, 18.0, 18.1, 25.5, 25.8, 36.7, 41.8, 42.6, 47.6, 70.1, 70.8, 71.4, 105.1, 111.9, 115.7, 117.3, 125.0, 129.3, 134.7, 134.9, 135.3, 145.1, 157.1, 160.1; HRMS (ESI) calcd for $C_{35}H_{62}O_6Si_2Na$ [M+Na$^+$]: 669.3983, found: 669.3971.

*4.1.29. Enone rac-**45**.* Macrolactonisation of the ester *rac*-**44** (60 mg, 92.7 μmol) was performed with NaH in the same manner described above. Purification by flash chromatography with 2.5% EtOAc/petrol as eluent afforded macrolactone (42 mg, 77%) as a colourless oil: ^{1}H NMR (300 MHz) δ 0.02 (s, 3H, SiMe), 0.05 (s, 3H, SiMe), 0.88 (s, 9H, SiCMe$_3$), 0.98–1.19 (m, 21H, Si(CHMe$_2$)$_3$), 1.58–1.65 (m, 2H, H14), 1.78 (ddd, *J*=13.8, 4.8, 2.4 Hz, 1H, H12), 1.93 (m, 1H, H12), 2.41 (dd, *J*=6.9, 6.3 Hz, 2H, H1′), 3.42 (dd, *J*=16.5, 2.1 Hz, 1H, H8), 3.70 (m, 1H, H13), 3.87 (dd, *J*=16.5, 6.6 Hz, 1H, H8), 4.43 (br m, 1H, H11), 5.08–5.13 (m, 2H, H3′), 5.24 (br dd, *J*=15.6, 5.1 Hz, 1H, H10), 5.36 (app quint, *J*=5.4 Hz, 1H, H15), 5.62 (dddd, *J*=15.6, 6.9, 2.4, 0.6 Hz, 1H, H9), 5.78 (dddd, *J*=17.7, 9.6, 7.2, 7.2 Hz, 1H, H2′), 6.72 (dd, *J*=7.5, 0.9 Hz, 1H, H4), 6.91 (dd, *J*=8.1, 0.9 Hz, 1H, H6), 7.32 (t, *J*=7.8 Hz, 1H, H5), 11.42 (br s, 1H, ArO*H*); ^{13}C NMR (100 MHz) δ −5.0, −4.1, 12.3, 17.9, 18.1, 18.11, 25.9, 39.0, 39.5, 42.9, 45.3, 66.5, 70.2, 74.5, 112.2, 116.7, 118.5, 123.3, 130.6, 131.5, 132.9, 134.3, 143.0, 163.3, 170.8; HRMS (ESI) calcd for $C_{33}H_{56}O_5Si_2Na$ [M+Na$^+$]: 611.3564, found: 611.3573.

Deprotection of the above racemic lactone (60 mg, 102 μmol) with TBAF was performed in the same manner described above. Purification by flash chromatography with 30% EtOAc/CH_2Cl_2 as eluent afforded the triol (30 mg, 92%) as a colourless crystalline solid: ^{1}H NMR (300 MHz) δ 1.68–1.80 (m, 2H, H14), 1.85–1.98 (m, 2H, H12), 2.40–2.59 (m, 2H, H1′), 3.18 (br d, *J*=14.4 Hz, 1H, H8), 3.87 (br m, 1H, H13), 4.01 (dd, *J*=14.4, 9.9 Hz, 1H, H8), 4.59 (br m, 1H, H11), 5.19 (d, *J*=9.9 Hz, 1H, H3′), 5.21 (dd, *J*=17.1, 1.5 Hz, 1H, H3′), 5.27 (m, 1H, H15), 5.37–5.50 (m, 2H, H9. H10), 5.86 (dddd, *J*=17.1, 9.9, 7.5, 6.9 Hz, 1H, H2′), 6.77 (d, *J*=7.5 Hz, 1H, H4), 6.83 (d, *J*=8.1 Hz, 1H, H6), 7.23 (t, *J*=7.8 Hz, 1H, H5); ^{13}C NMR (75 MHz) δ 37.8, 39.7, 40.2, 40.4, 62.8, 69.2, 71.1, 116.0, 118.2, 119.3, 122.9, 125.4, 132.3, 133.3, 136.1, 141.3, 155.8, 165.5; HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ [M+Na$^+$]: 341.1365, found: 341.1368.

To a stirred solution of the racemic triol (45 mg, 141 μmol) in CH_2Cl_2 (6 mL) was added MnO_2 (247 mg, 2.82 mmol). The resulting mixture was stirred overnight at rt and then diluted with CH_2Cl_2 and filtered through Celite. Concentration of the filtrate under reduced pressure and purification of the crude residue by flash chromatography using 20% EtOAc/CH_2Cl_2 as eluent afforded the ketone enone *rac*-**45** (15 mg, 60% based on recovered starting material (20 mg)) as a pale yellow gum: ^{1}H NMR (300 MHz) δ 1.73 (ddd, *J*=15.9, 6.8, 2.7 Hz, 1H, H14), 1.84 (ddd, *J*=15.9, 9.8, 1.8 Hz, 1H, H14), 2.45–254 (m, 3H, H12, H1′), 2.83 (dd, *J*=14.6, 4.7 Hz, 1H, H12), 3.63 (ddd, *J*=17.7, 5.1, 1.5 Hz, 1H, H8), 3.80 (ddd, *J*=17.7, 4.8, 2.1 Hz, 1H, H8), 4.16 (m, 1H, H13), 5.13–5.18 (m, 2H, H3′), 5.49 (m, 1H, H15), 5.79 (dddd, *J*=17.4, 10.2, 7.2, 6.9 Hz, 1H, H2′), 5.95 (ddd, *J*=16.2, 2.1, 1.5 Hz, 1H, H10), 6.51 (ddd, *J*=16.2, 5.1, 4.8 Hz, 1H, H9), 6.73 (dd, *J*=7.5, 0.9 Hz, 1H, H4), 6.93 (dd, *J*=8.1, 0.9 Hz, 1H, H6), 7.33 (dd, *J*=8.1, 7.5 Hz, 1H, H5), 10.2 (s, 1H, ArO*H*); ^{13}C NMR (75 MHz) δ 39.1, 39.5, 41.4, 51.2, 66.8, 74.9, 114.3, 117.4, 119.2, 123.9, 131.7, 132.7, 134.3, 139.0, 144.1, 161.4, 169.7, 200.5; HRMS (ESI) calcd for $C_{18}H_{20}O_5Na$ [M+Na$^+$]: 339.1208, found: 339.1205.

*4.1.30. Alkene rac-**46**.* Stille coupling between the racemic vinyl stannane **36** (342 mg, 459 μmol) and the benzyl bromide **7** (138 mg, 595 μmol) was performed in the same manner as described above. Purification by flash chromatography with 5–10% EtOAc/petrol as eluent afforded the ester *rac*-**46** (240 mg, 81%) as a colourless oil: IR ν_{max} (film) 3477, 3055, 2945, 2893, 2866, 1737, 1607, 1267, 1076, 1052, 976, 884, 838 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.04 (s, 3H, SiMe), 0.05 (s, 3H, SiCMe), 0.87 (s, 9H, SiCMe$_3$), 1.00 (s, 21H, Si(CHMe$_3$)), 1.53–1.63 (m, 2H, H7′), 1.69 (s, 3H, H9), 1.70 (s, 3H, H9), 1.71 (ddd, *J*=13.2, 9.0, 4.0 Hz, 1H, H5′), 1.99 (ddd, *J*=13.2, 10.0, 5.0 Hz, 1H, H5′), 2.13 (ddd, *J*=13.6, 7.2, 6.8 Hz, 1H, H9′), 2.25 (ddd, *J*=13.6, 6.8, 6.8 Hz, 1H, H9′), 3.51 (s, 1H, O*H*), 3.79–3.89 (m, 2H, H1′), 3.91 (m, 1H, H8′), 4.01 (br m, 1H, H6′), 4.06 (ddd, *J*=9.0, 8.4, 5.0 Hz, 1H, H4′), 5.05–5.11 (m, 2H, H11′), 5.39 (dd, *J*=15.6, 8.4 Hz, 1H, H3′), 5.76 (ddd, *J*=15.6, 7.2, 6.4 Hz, 1H, H2′), 5.81 (dddd, *J*=17.2, 10.4, 7.2, 6.8 Hz, 1H, H10′), 6.83 (d, *J*=8.0 Hz, 1H, H8), 6.91 (d, *J*=7.6 Hz, 1H, H6), 7.41 (t, *J*=8.0 Hz, 1H, H7); ^{13}C NMR (100 MHz) δ −4.9, −4.6, 12.4, 17.9, 18.06, 18.1, 25.5, 25.8, 36.7, 40.4, 42.3, 44.9, 67.8, 68.9, 71.4, 105.1, 111.9, 115.7, 117.2, 125.1, 129.4, 134.6, 135.0, 135.3, 145.0, 157.1, 160.1; HRMS (ESI) calcd for $C_{35}H_{62}O_6Si_2Na$ [M+Na$^+$]: 669.3983, found: 669.3969.

*4.1.31. Enone rac-**47**.* Macrolactonisation of the ester *rac*-**46** (115 mg, 178 μmol) was performed with NaH in the same manner described above. Purification by flash chromatography with 2.5% EtOAc/petrol as eluent afforded macrolactone (75 mg, 72%) as a colourless oil: IR ν_{max} (film) 2956, 2930, 2866, 1657, 1251, 1049, 975, 836 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.05 (s, 6H, SiMe$_2$), 0.88 (s, 9H, SiCMe$_3$), 1.01–1.06 (m, 3H, Si(C*H*Me$_2$)$_3$), 1.04 (s, 18H, Si(CHMe$_2$)$_3$), 1.69 (ddd, *J*=13.8, 9.6, 1.8 Hz, 1H, H14), 1.99 (m, 2H, H12, H14), 2.23 (ddd, *J*=15.9, 6.8, 3.5 Hz, 1H, H12), 2.45 (dd, *J*=6.9, 6.3 Hz, 2H, H1′), 3.58 (br d, *J*=16.2 Hz, 1H, H8), 3.68 (dd, *J*=16.2, 5.4 Hz, 1H, H8), 4.24 (m, 1H, H13), 4.49 (app t, *J*=6.0 Hz, 1H, H11), 5.07–5.14 (m, 2H, H3′), 5.34 (dd, *J*=15.6, 6.0 Hz, 1H, H10), 5.40–5.48 (m, 2H, H9, H15), 5.81 (m, 1H, H2′), 6.73 (d, *J*=7.8 Hz, 1H, H4), 6.88 (dd, *J*=8.1, 1.2 Hz, 1H, H6), 7.28 (dd, *J*=8.1, 7.8 Hz, 1H, H5), 10.19 (br s, 1H, ArO*H*); ^{13}C NMR (100 MHz) δ −4.7, −4.4, 12.2, 18.0, 18.1, 18.11, 25.9, 38.8, 39.1, 40.2, 44.5, 65.5, 70.0, 72.0, 114.8, 116.4, 118.5, 122.9, 127.2, 133.6, 133.62, 135.5, 142.0, 161.0, 169.7; HRMS (ESI) calcd for $C_{33}H_{56}O_5Si_2Na$ [M+Na$^+$]: 611.3564, found: 611.3563.

Deprotection of the above racemic lactone (150 mg, 255 μmol) with TBAF was performed in the same manner described above. Purification by flash chromatography with 30% EtOAc/CH_2Cl_2 as eluent afforded the triol (65 mg, 80%) as a colourless crystalline solid: mp 171–172; ^{1}H NMR (300 MHz, CD_3OD) δ 1.50 (ddd, J=15.6, 7.8, 0.9 Hz, 1H, H14), 1.63–1.88 (m, 3H, H12, H14), 2.27–2.47 (m, 2H, H1′), 3.42 (ddd, J=16.5, 3.6, 2.1 Hz, 1H, H8), 3.56 (dd, J=16.5, 7.5 Hz, 1H, H8), 3.89 (br m, 1H, H13), 4.05 (m, 1H, H11), 5.01–5.11 (m, 2H, H3′), 5.27–5.37 (m, 2H, H10, H15), 5.50 (ddd, J=15.6, 7.5, 3.6 Hz, 1H, H9), 5.93 (dddd, J=17.1, 10.2, 7.5, 6.6 Hz, 1H, H2′), 6.64 (d, J=7.8 Hz, 1H, H4), 6.70 (d, J=8.1 Hz, 1H, H6), 7.12 (dd, J=8.1, 7.8 Hz, 1H, H5); ^{13}C NMR (100 MHz, CD_3OD) δ 38.3, 40.9, 42.9, 44.5, 67.9, 71.4, 75.9, 115.7, 118.0, 121.8, 122.7, 131.6, 132.2, 134.8, 135.3, 140.7, 158.0, 170.9; HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ [M+Na$^+$]: 341.1365, found: 341.1370.

Oxidation of the above racemic triol (30 mg, 94.2 μmol) was performed with MnO_2 in the same manner as described above. Purification by flash chromatography with 20% EtOAc/CH_2Cl_2 as eluent afforded the enone *rac*-**47** (6 mg, 27% based on recovered starting material (8 mg)) as a pale yellow gum: ^{1}H NMR (300 MHz) δ 1.75 (ddd, J=15.9, 7.2, 2.9 Hz, 1H, H14), 2.21 (ddd, J=15.9, 3.9, 3.9 Hz, 1H, H14), 2.58 (dd, J=15.0, 9.9 Hz, 2H, H1′), 2.76 (dd, J=15.0, 9.9 Hz, 1H, H12), 2.80 (dd, J=15.0, 4.8 Hz, 1H, H12), 3.36 (dt, J=18.8, 2.7 Hz, 1H, H8), 4.29 (dd, J=18.8, 6.6 Hz, 1H, H8), 4.40 (m, 1H, H13), 5.26 (m, 1H, H15), 5.30 (m, 2H, H3′), 5.89 (m, 1H, H2′), 5.99 (d, J=15.9 Hz, 1H, H10), 6.77 (d, J=7.5 Hz, 1H, H4), 6.87 (ddd, J=15.9, 6.6, 3.3 Hz, 1H, H9), 6.91 (d, J=8.1 Hz, 1H, H6), 7.03 (s, 1H, ArO*H*), 7.31 (dd, J=8.1, 7.5 Hz, 1H, H5); ^{13}C NMR (75 MHz) δ 36.9, 37.5, 38.2, 50.9, 64.1, 73.6, 116.9, 117.8, 119.2, 123.4, 128.3, 133.1, 134.6, 138.3, 146.3, 155.9, 160.6, 198.7; HRMS (ESI) calcd for $C_{18}H_{20}O_5Na$ [M+Na$^+$]: 339.1208, found: 339.1202.

*4.1.32. Alcohols (−)-**34** and (−)-**35**.* To a solution of (−)-β-methoxydiisopinocamphenyl-borane[25] (8.51 g, 26.4 mmol) in Et_2O (43 mL) at 0 °C was added, dropwise, allyl magnesium bromide (25.1 mL, 25.1 mmol, 1.0 M in hexanes). The resulting mixture was allowed to warm to rt and stirred for 1 h before the solvents were removed under vacuum. To the resulting residue was added pentane (19 mL×3) and the precipitated magnesium salts were removed by filtration. The filtrate was concentrated under vacuum and the resulting allylborane was redissolved in Et_2O (47 mL) and cooled to −100 °C. A solution of the crude aldehyde (derived from oxidation of *rac*-**13**) (6.40 g, 13.2 mmol) in Et_2O (7 mL) at −78 °C was added dropwise to the solution of borane. After stirring for 2 h at −100 °C, the reaction mixture was allowed to warm to −78 °C and then quenched with MeOH (8 mL) and warmed to rt. 2 M NaOH (8 mL) and 30 wt % aqueous H_2O_2 (6.8 mL) were added and the resulting mixture was stirred overnight. The usual workup and purification of the crude product by flash chromatography using 2.5% EtOAc/petrol as eluent yielded the optically active allyl alcohol (−)-**29** (2.75 g, 40%): $[\alpha]_{D^{27}}$ −14.72 (*c* 1.45, CH_2Cl_2). Further elution gave mixed fraction (530 mg, 8%) followed by (−)-**28** (2.83 g, 41%): $[\alpha]_{D^{27}}$ −0.21 (*c* 1.05, CH_2Cl_2).

The TMS deprotection of the above alkyne (−)-**29** (1.20 g, 2.45 mmol) was performed in the same manner as described above to give the alkyne (−)-**35** (1.08, 97%): $[\alpha]_{D^{26}}$ −8.75 (*c* 1.00, CH_2Cl_2).

The TMS deprotection of the optically active TMS acetylene (−)-**28** (2.19 g, 4.16 mmol) was performed in the same manner as described above to give the alkyne (−)-**34** (1.65, 87%): $[\alpha]_{D^{26}}$ −6.35 (*c* 1.14, CH_2Cl_2).

*4.1.33. Stannanes (−)-**37** and (+)-**36**.* Hydrostannylation of the optically active alkyne (−)-**34**(1.55 g, 3.41 mmol) was performed in the same manner to that described above to give the vinyl stannane (−)-**37**(2.13 g, 84%): $[\alpha]_{D^{27}}$ −15.62 (*c* 1.15, CH_2Cl_2).

Hydrostannylation of the optically active alkyne (−)-**35** (1.08 g, 2.37 mmol) was performed in the same manner to that described above to give the vinyl stannane (+)-**36** (1.56 g, 88%): $[\alpha]_{D^{27}}$ +3.66 (*c* 2.52, CH_2Cl_2).

*4.1.34. Alkenes (−)-**44** and (+)-**46**.* Stille coupling between the optically active vinyl stannane (−)-**37** (532 mg, 712 μmol) and the benzyl bromide (250 mg, 1. 06 mmol) was performed in the same manner as described above to give the ester (−)-**44** (388 mg, 84%): $[\alpha]_{D^{28}}$ −17.6 (*c* 1.07, CH_2Cl_2).

Stille coupling between the optically active vinyl stannane (+)-**36** (405 mg, 566 μmol) and the benzyl bromide (163 mg, 736 μmol) was performed in the same manner as described above to give the alkene (+)-**46** (313 mg, 89%): $[\alpha]_{D^{29}}$ +12.2 (*c* 1.19, CH_2Cl_2).

*4.1.35. Enone (+)-**48**.* To a suspension of pentane-washed NaH (528 mg, 22.1 mmol, 60% dispersion in mineral oil) in THF (12.5 mL) was added dropwise the ester (−)-**44** (125 mg, 190 μmol) in THF (3 mL). After stirring for 2 h at 40 °C, when all the starting material consumed by TLC analysis, methyl iodide (362 μL, 3.88 mmol) was added dropwise and the resulting mixture was stirred overnight at rt. Et_2O was added and the reaction mixture was then cooled to 0 °C and acidified to pH 3 with cold 5% aqueous HCl. The usual workup produced a residue, which was purified on silica gel using 2.5% EtOAc/petrol as eluent to give the macrolactone (89 mg, 76%) as a colourless oil: $[\alpha]_{D^{25}}$ +47.87 (*c* 0.75, CH_2Cl_2); IR ν_{max} (film) 3054, 2946, 2895, 2867, 1720, 1644, 1266, 1090, 982, 884, 837 cm^{-1}; ^{1}H NMR (400 MHz,) δ 0.01 (s, 3H, SiMe), 0.02 (s, 3H, SiMe), 0.86 (s, 9H, $SiCMe_3$), 1.02, (d, J=4.0 Hz, 21H, $Si(CHMe_2)_3$), 1.86 (dd, J=14.0, 2.8 Hz, 1H, H14), 1.88 (dd, J=14.0, 2.4 Hz, 1H, H14), 1.99–2.07 (m, 2H, H12), 2.44–2.56 (m, 2H, H1′), 3.19 (app ddd, J=15.6, 2.0, 2.0 Hz, 1H, H8), 3.69 (dd, J=15.6, 8.8 Hz, 1H, H8), 3.79 (s, 3H, OCH_3), 4.10 (m, 1H, H13), 4.53 (br m, 1H, H11), 5.04 (m, 1H, H15), 5.10 (dd, J=10.0, 1.6 Hz, 1H, H3′), 5.13 (dd, J=16.8, 1.6 Hz, 1H, H3′), 5.43 (dd, J=15.6, 5.2 Hz, 1H, H10), 5.67 (ddd, J=15.6, 8.4, 3.2 Hz, 1H, H9), 5.90 (dddd, J=16.8, 10.0, 7.2, 6.8 Hz, 1H, H2′), 6.79 (d, J=7.2 Hz, 1H, H4), 6.80 (d, J=8.4 Hz, 1H, H6), 7.25 (t, J=8.0 Hz, 1H, H5); ^{13}C NMR (100 MHz_3) δ 4.5, −4.1, 12.3, 18.0, 18.1, 18.2, 26.0, 36.8, 38.1, 39.6, 43.9, 55.6, 65.4, 69.2, 72.6, 109.5, 117.2, 122.4, 124.5, 126.4, 130.2, 134.4, 136.3, 138.7, 156.5, 168.3; HRMS (ESI) calcd for $C_{34}H_{58}O_5Si_2Na$ [M+Na$^+$]: 625.3720, found: 625.3730.

Deprotection of the optically active lactone (80 mg, 133 μmol) was performed in the same manner described above to give the diol (40 mg, 91%) as a colourless crystalline solid: mp 126–127 °C; $[\alpha]_{D^{26}}$ +22.23 (*c* 0.85, CH_2Cl_2); IR ν_{max} (film) 3359, 3057, 2947, 2924, 2842, 1715, 1643, 1266, 993, 896 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.66 (ddd, J=14.0, 11.2, 2.4 Hz, 1H, H14), 1.73 (m, 1H, H14), 1.87–1.96 (m, 2H, H12), 2.05 (br s, 1H, O*H*), 2.44–2.57 (m, 2H, H1′), 3.19 (dddd, J=14.0, 3.2, 2.8, 2.4 Hz, 1H, H8), 3.79 (dd, J=14.0, 10.8 Hz, 1H, H8), 3.80 (s, 3H, OCH_3), 3.98 (br m, 1H, H13), 4.6 (br m, 1H, H11), 4.97 (dddd, J=11.2, 6.4, 5.6, 2.6 Hz, 1H, H15), 5.11–5.17 (m, 2H, H3′), 5.47 (ddd, J=15.6, 2.4, 2.4 Hz, 1H, H10), 5.64 (dddd, J=15.6, 10.8, 3.2, 2.0 Hz, 1H, H9), 5.90 (dddd, J=17.2, 10.0, 7.2, 7.2 Hz, 1H, H2′), 6.81 (d, J=7.2 Hz, 1H, H4), 6.83 (d, J=8.4 Hz, 1H, H6), 7.27 (t, J=7.8 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ 37.5, 39.1, 39.8, 40.3, 55.8, 62.9, 69.0, 71.0, 109.9, 118.0, 122.7, 123.6, 125.6, 130.6, 133.4, 135.6, 138.9, 157.2, 167.6; HRMS (ESI) calcd for $C_{19}H_{24}O_5Na$ [M+Na$^+$]: 355.1521, found: 355.1523.

Oxidation of the racemic allylic alcohol (13 mg, 44.5 μmol) was performed in the same manner described above. Purification by flash chromatography with 20% EtOAc/CH_2Cl_2 as eluent afforded the enone (+)-**48** (7 mg, 71% base on recovered starting material (3 mg)) as a pale yellow gum: IR ν_{max} (film) 3453, 3057, 3010, 2961, 2842, 1722, 1662, 1626, 1267, 988, 897 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.91–2.03 (m, 2H, H14), 2.24 (d, J=6.0 Hz, 1H, O*H*), 2.55 (dd, J=6.8, 6.4 Hz, 2H, H1′), 2.71 (dd, J=13.2, 7.8 Hz, 1H, H12), 2.92 (dd, J=13.2, 4.8 Hz, 1H, H12), 3.41 (ddd, J=16.8, 4.6, 2.0 Hz, 1H, H8), 3.82 (s, 3H, OCH_3), 3.93 (dd, J=16.8, 8.8 Hz, 1H, H8), 4.29 (m, 1H, H13), 5.02 (m, 1H, H15), 5.15 (d, J=10.0 Hz, 1H, H3′), 5.17 (d, J=17.2 Hz, 1H, H3′), 5.89 (dddd, J=17.2, 10.0, 7.2, 6.8 Hz, 1H, H2′), 6.13 (d, J=16.0 Hz, 1H, H10), 6.76 (ddd, J=16.0, 8.8, 4.6 Hz, 1H, H9), 6.82 (d, J=7.6 Hz, 1H, H4), 6.87 (d, J=8.4 Hz, 1H, H6), 7.31 (t, J=8.0 Hz, 1H, H5); ^{13}C NMR

(100 MHz) δ 37.0, 38.0, 39.4, 47.4, 55.7, 65.8, 72.4, 110.1, 118.1, 122.8, 123.8, 130.8, 133.1, 133.4, 136.5, 144.5, 157.0, 168.1, 200.5; HRMS (ESI) calcd for $C_{19}H_{22}O_5Na$ [M+Na$^+$]: 353.1365, found: 353.1365.

*4.1.36. Enone (−)-**49**.* Macrolactonisation and methylation of the ester (+)-**46** (741 mg, 1.15 mmol) with NaH and methyl iodide was performed in the same manner as described above and purification on silica gel using 2.5% EtOAc/petrol as eluent gave the lactone (534 mg, 77%) as a colourless oil: $[\alpha]_{D^{23}}$ +21.90 (*c* 1.90, CH_2Cl_2); IR ν_{max} (film) 3076, 3053, 2946, 2894, 2866, 1725, 1644, 1277, 1085, 975, 837 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.14 (s, 3H, SiMe), 0.22 (s, 3H, SiMe), 0.91 (s, 9H, SiC*Me*$_3$), 1.03 (s, 21H, Si(C*H*Me$_2$)$_3$), 1.58 (dd, *J*=15.2, 6.8 Hz, 1H, H14), 1.70 (ddd, *J*=12.8, 10.0, 3.6 Hz, 1H, H12), 1.73 (dd, *J*=15.2, 8.0 Hz, 1H, H14), 1.84 (ddd, *J*=12.8, 11.6, 5.2 Hz, 1H, H12), 2.30 (m, 1H, H1′), 2.46 (m, 1H, H1′), 3.37 (d, *J*=16.4 Hz, 1H, H8), 3.74 (ddd, *J*=16.4, 5.6, 2.4 Hz, 1H, H8), 3.80 (s, 3H, OC*H*$_3$), 4.03–4.11 (m, 2H, H11, H13), 5.09 (dd, *J*=10.0, 1.6 Hz, 1H, H3′), 5.13 (dd, *J*=17.2, 1.6 Hz, 1H, H3′), 5.28 (app q, *J*=7.2 Hz, 1H, H15), 5.42–5.50 (m, 2H, H9, H10), 5.88 (dddd, *J*=17.2, 10.0, 6.4, 6.0 Hz, 1H, H2′), 6.79 (d, *J*=7.6 Hz, 1H, H4), 6.81 (d, *J*=8.4 Hz, 1H, H6), 7.24 (t, *J*=8.0 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ −4.5, −4.1, 12.3, 17.9, 18.0, 18.1, 25.9, 36.8, 40.0, 42.5, 44.4, 55.5, 68.8, 72.1, 74.5, 109.4, 117.2, 122.7, 124.5, 129.6, 130.0, 134.2, 135.2, 138.5, 156.6, 167.9; HRMS (ESI) calcd for $C_{34}H_{58}O_5Si_2Na$ [M+Na$^+$]: 625.3720, found: 625.3716.

Deprotection of the lactone (160 mg, 265 μmol) was performed in the same manner as described above and purification on silica gel using 30% EtOAc/CH_2Cl_2 as eluent gave the diol (80 mg, 91%) as a crystalline solid: mp 123–124 °C; $[\alpha]_{D^{25}}$ +32.60 (*c* 1.23, CH_2Cl_2); IR ν_{max} (film) 3497, 3376, 3056, 2980, 2960, 2928, 2838, 1729, 1643, 1266, 896 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.72 (m, 1H, H14), 1.76 (ddd, *J*=14.0, 5.2, 3.2 Hz, 1H, H14), 1.87 (m, 2H, H12), 2.12 (d, *J*=2.0 Hz, 1H, O*H*), 2.36–2.51 (m, 2H, H1′), 3.27 (br d, *J*=15.6 Hz, 1H, H8), 3.76 (dd, *J*=15.6, 8.8 Hz, 1H, H8), 3.79 (s, 3H, OC*H*$_3$), 4.08 (m, 1H, H13), 4.31 (br m, 1H, H11), 5.10 (dd, *J*=10.4, 1.6 Hz, 1H, H3′), 5.13 (dd, *J*=17.2, 1.6 Hz, 1H, H3′), 5.41 (ddd, *J*=15.6, 6.8, 1.6 Hz, 1H, H10), 5.47 (m, 1H, H15), 5.62 (ddd, *J*=15.6, 8.8, 2.8 Hz, 1H, H9), 5.89 (dddd, *J*=17.2, 10.4, 7.2, 6.8 Hz, 1H, H2′), 6.78 (d, *J*=7.6 Hz, 1H, H4), 6.82 (d, *J*=8.4 Hz, 1H, H6), 7.27 (t, *J*=8.0 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ 36.4, 39.6, 41.3, 44.8, 55.5, 66.9, 70.8, 74.5, 109.6, 117.8, 122.9, 123.9, 128.5, 130.6, 133.6, 133.6, 134.9, 138.8, 157.0, 168.2; HRMS (ESI) calcd for $C_{19}H_{24}O_5Na$ [M+Na$^+$]: 355.1521, found: 355.1520.

To a stirred solution of the optically active diol (100 mg, 301 μmol) in CH_2Cl_2 (12 mL) was added MnO_2 (527 mg, 6.02 mmol). The resulting suspension was stirred overnight at rt and then diluted with CH_2Cl_2 and filtered through Celite. Concentration of the filtrate under reduced pressure and purification of the crude residue by flash chromatography using 20% EtOAc/CH_2Cl_2 as eluent afforded the enone (−)-**49** (66 mg, 72% based on recovered starting material (16 mg)) as a pale yellow gum: $[\alpha]_{D^{24}}$ −18.43 (*c* 0.91, CH_2Cl_2); IR ν_{max} (film) 3460, 3056, 2986, 2931, 2842, 1720, 1660, 1633, 1266, 984, 896 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.67 (ddd, *J*=16.0, 6.8, 6.4 Hz, 1H, H14), 1.93 (ddd, *J*=16.0, 5.6, 2.4 Hz, 1H, H14), 2.40–2.50 (m, 2H, H1′), 2.65 (dd, *J*=13.2, 8.6 Hz, 1H, H12), 2.97 (dd, *J*=13.2, 4.0 Hz, 1H, H12), 3.43 (ddd, *J*=16.0, 4.0, 2.0 Hz, 1H, H8), 3.80 (s, 3H, OC*H*$_3$), 3.85 (dd, *J*=16.0, 10.0 Hz, 1H, H8), 4.37 (m, 1H, H13), 5.11–5.19 (m, 3H, H3′, H15), 5.85 (dddd, *J*=17.2, 10.0, 6.8, 6.8 Hz, 1H, H2′), 6.23 (dd, *J*=16.0, 1.6 Hz, 1H, H10), 6.68 (ddd, *J*=16.0, 10.0, 4.0 Hz, 1H, H9), 6.81–6.86 (m, 2H, H4, H6), 7.30 (t, *J*=8.0 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ 73.0, 39.8, 41.7, 48.0, 55.7, 69.1, 73.6, 110.1, 118.4, 122.9, 124.1, 130.7, 133.0, 133.9, 136.6, 143.4, 157.0, 168.2, 200.6; HRMS (ESI) calcd for $C_{19}H_{22}O_5Na$ [M+Na$^+$]: 353.1365, found: 353.1372.

*4.1.37. trans-Pyranone (+)-**50**.* To a stirred solution of the optically active enone (+)-**48** (26 mg, 78.7 μmol) in deuterochloroform (2.5 mL) was added amberlyst-15 resin (104 mg). The resulting suspension was heated under reflux for 18 h, then filtered and the solvent was concentrated under reduced pressure. Purification of the crude residue on silica gel using 10% EtOAc/CH_2Cl_2 as eluent yielded the *trans*-pyranone (+)-**50** (23.5 mg, 90%) as a colourless crystalline solid.

To a stirred solution of the optically active enone (−)-**49** (41 mg, 124 μmol) in deuterochloroform (4 mL) was added amberlyst-15 resin (164 mg). The resulting suspension was heated under reflux for 23 h, then filtered and the solvent concentrated under reduced pressure. Purification of the crude residue on silica gel using 10% EtOAc/CH_2Cl_2 as eluent yielded the *trans*-pyranone (+)-**50** (32 mg, 78%) as a colourless crystalline solid: mp 182–183 °C; $[\alpha]_{D^{16}}$ +138 (*c* 0.53, $CHCl_3$), lit.[11b] (enantiomer) $[\alpha]_{D^{22}}$ −140 (*c* 0.60, $CHCl_3$); IR ν_{max} (film) 3057, 2960, 2927, 2854, 1719, 1644, 1599, 1471, 1266, 1117, 1074 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.72 (ddd, *J*=14.8, 3.2, 1.2 Hz, 1H, H14), 1.83 (ddd, *J*=14.8, 11.2, 10.0 Hz, 1H, H14), 2.22 (dd, *J*=17.6, 10.8 Hz, 1H, H12), 2.37 (m, 1H, H1′), 2.43 (dd, *J*=17.6, 3.6 Hz, 1H, H12), 2.48 (m, 1H, H1′), 2.483 (dd, *J*=14.0, 2.0 Hz, 1H, H8), 2.55 (dd, *J*=15.2, 8.8 Hz, 1H, H10), 2.66 (dd, *J*=15.2, 6.5 Hz, 1H, H10), 3.46 (dd, *J*=14.0, 11.4 Hz, 1H, H8), 3.81 (s, 3H, OC*H*$_3$), 4.25 (dddd, *J*=11.4, 8.8, 6.5, 2.0 Hz, 1H, H9), 4.50 (app dt, *J*=10.0, 3.6 Hz, 1H, H13), 5.15, (dd, *J*=10.0, 1.6 Hz, 1H, H3′), 5.18 (dd, *J*=16.8, 1.6 Hz, 1H, H3′), 5.63 (dddd, *J*=11.2, 8.4, 5.2, 3.2 Hz, 1H, H15), 5.88 (dddd, *J*=16.8, 10.0, 7.2, 6.8 Hz, 1H, H2′), 6.79 (d, *J*=7.6 Hz, 1H, H4), 6.84 (d, *J*=8.4 Hz, 1H, H6), 7.28 (dd, *J*=8.4, 7.6 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ 38.9, 39.0, 40.1, 47.1, 55.8, 68.1, 72.1, 74.0, 110.0, 118.0, 122.6, 125.6, 130.5, 133.3, 147.0, 155.9, 169.8, 207.1; HRMS (ESI) calcd for $C_{19}H_{22}O_5Na$ [M+Na$^+$]: 353.1365, found: 353.1372.

*4.1.38. Alcohols (+)-**51** and (+)-**52**.* To a stirred solution of the pyranone (+)-**50** (30 mg, 90.8 μmol) in MeOH (5 mL) was added $NaBH_4$ (14 mg, 363 μmol) at −78 °C. After stirring for 30 min at −78 °C, the reaction mixture was warmed to 0 °C and then EtOAc and water were added. The usual workup produced a residue, which was purified on silica gel using 20% EtOAc/CH_2Cl_2 as eluent to give the alcohol (+)-**51** (13 mg, 43%) as colourless oil: $[\alpha]_{D^{19}}$ +18.09 (*c* 0.63, $CHCl_3$); IR ν_{max} (film) 3427, 3056, 2978, 2924, 2857, 1715, 1470, 1266, 1114, 1096, 1073, 996, 897 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.36 (ddd, *J*=12.4, 8.0, 7.6 Hz, 1H, H14), 1.59 (d, *J*=6.0 Hz, 1H, O*H*), 1.71 (dd, *J*=14.4, 4.0 Hz, 1H, H12), 1.78–1.89 (m, 3H, H10, H12), 1.90 (ddd, *J*=12.4, 5.0, 3.0 Hz, 1H, H14), 2.34 (dd, *J*=14.0, 1.8 Hz, 1H, H8), 2.35 (m, 1H, H1′), 2.47 (ddd, *J*=14.8, 8.0, 6.8 Hz, 1H, H1′), 3.37 (dd, *J*=14.0, 12.0 Hz, 1H, H8), 3.79 (s, 3H, OC*H*$_3$), 3.94–4.02 (m, 2H, H11, H13), 4.17 (m, 1H, H9), 5.12–5.19 (m, 2H, H3′), 5.60 (m, 1H, H15), 5.87 (dddd, *J*=17.2, 10.0, 6.8, 6.8 Hz, 1H, H2′), 6.80 (d, *J*=7.2 Hz, 1H, H4), 6.81 (d, *J*=9.2 Hz, 1H, H6), 7.26 (dd, *J*=9.2, 7.2 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ 36.2, 37.7, 38.9, 40.6, 41.0, 55.8, 65.4, 66.9, 73.1, 74.8, 109.5, 117.7, 122.7, 125.7, 130.2, 133.5, 138.6, 155.6, 170.3; HRMS (ESI) calcd for $C_{19}H_{24}O_5Na$ [M+Na$^+$]: 355.1521, found: 355.1517.

Further elution afforded a fraction of mixed alcohols (+)-**51** and (+)-**52** (3 mg, 10%). Further elution then gave the desired alcohol (+)-**52** (14 mg, 46%) as a colourless oil: $[\alpha]_{D^{19}}$ +10.7 (*c* 0.49, $CHCl_3$), lit. (enantiomer)[11b] $[\alpha]_{D^{20}}$ −10.6 (*c* 1.50, $CHCl_3$); IR ν_{max} (film) 3427, 3056, 2942, 2924, 2841, 1716, 1470, 1266, 1115, 1095, 1072, 996, 896 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.51–1.59 (m, 3H, H12, H14), 1.78 (ddd, *J*=12.8, 6.6, 6.0 Hz, 1H, H10), 1.91 (ddd, *J*=14.8, 11.4, 10.8 Hz, 1H, H12), 1.99 (ddd, *J*=12.8, 4.4, 4.4 Hz, 1H, H10), 2.34 (ddd, *J*=14.4, 6.8, 5.6 Hz, 1H, H1′), 2.45 (m, 1H, H1′), 2.46 (d, *J*=14.8 Hz, 1H, H8), 3.39 (dd, *J*=14.8, 10.0 Hz, 1H, H8), 3.79 (s, 3H, OC*H*$_3$), 3.97–4.08 (m, 2H, H11, H13), 4.32 (m, 1H, H9), 5.10–5.18 (m, 2H, H3′), 5.59 (dddd, *J*=13.2, 10.8, 5.6, 2.4 Hz, 1H, H15), 5.87 (dddd, *J*=17.2, 10.4, 7.2, 6.8 Hz, 1H, H2′), 6.73 (d, *J*=7.6 Hz, 1H, H4), 6.78 (d, *J*=8.0 Hz, 1H, H6), 7.22 (t, *J*=8.0 Hz, 1H, H5); ^{13}C NMR (100 MHz) δ 38.1, 38.7, 38.9, 39.4, 39.6, 55.8, 65.1, 67.5, 72.6, 72.8, 109.4, 117.7, 122.8, 125.4, 129.9, 133.6, 138.4, 155.9, 169.1; HRMS (ESI) calcd for $C_{19}H_{24}O_5Na$ [M+Na$^+$]: 355.1521, found: 355.1517.

*4.1.39. Mitsunobu inversion of alcohol (+)-**51**.* To a stirred solution of the undesired alcohol (+)-**51** (20 mg, 60.5 μmol) in benzene (2 mL) at rt was added PPh_3 (68 mg, 303 μmol), 4-nitrobenzoic acid (37 mg, 266 μmol) and DEAD (40 μL, 303 μmol). The resulting mixture was stirred for 2 h at rt, and then the volatiles were concentrated under reduced pressure. The crude residue was purified by flash chromatography using 2.5% EtOAc/petrol as eluent to afford the *p*-nitrobenzoate ester (28 mg, 96%) as a colourless oil: $[\alpha]_{D^{25}}$ −3.84 (*c* 0.46, $CHCl_3$); IR ν_{max} (film) 3057, 2959, 2928, 1722, 1529, 1269, 1116, 1071, 1047, 874 cm^{-1}; ^1H NMR (400 MHz) δ 1.67 (app dt, *J*=14.8, 1.6 Hz, 1H, H14), 1.80–1.93 (m, 3H, H10, H12), 1.94 (dd, *J*=14.8, 10.8 Hz, 1H, H14), 2.21 (ddd, *J*=13.6, 6.0, 4.0 Hz, 1H, H10), 2.36 (ddd, *J*=14.4, 7.2, 5.4 Hz, 1H, H1′), 2.43 (d, *J*=14.6 Hz, 1H, H8), 2.48 (ddd, *J*=14.4, 8.0, 6.8 Hz, 1H, H1′), 3.58 (dd, *J*=14.6, 10.8 Hz, 1H, H8), 3.81 (s, 3H, OCH_3), 4.15 (m, 1H, H9), 4.44 (dt, *J*=9.6, 4.0 Hz, 1H, H13), 5.13 (d, *J*=9.8 Hz, 1H, H3′), 5.17 (dd, *J*=17.2, 1.6 Hz, 1H, H3′), 5.40 (m, 1H, H11), 5.63 (dddd, *J*=10.8, 8.0, 5.4, 3.2 Hz, 1H, H15), 5.87 (dddd, *J*=17.2, 9.8, 7.2, 6.8 Hz, 1H, H2′), 6.76 (d, *J*=7.6 Hz, 1H, H4), 6.81 (d, *J*=8.4 Hz, 1H, H6), 7.25 (dd, *J*=8.4, 7.6 Hz, 1H, H5), 8.23 (d, *J*=8.8 Hz, 2H, 2× H7′), 8.31 (d, *J*=8.8 Hz, 2H, 2× H6′); ^{13}C NMR (100 MHz) δ 34.1, 35.4, 38.4, 39.0, 39.1, 55.8, 65.7, 69.8, 73.0, 73.3, 109.6, 117.8, 122.7, 123.7, 125.5, 130.2, 130.7, 133.4, 135.6, 138.2, 150.6, 155.9, 164.0, 169.8; HRMS (ESI) calcd for $C_{26}H_{27}NO_8Na$ [M+Na^+]: 504.1634, found: 504.1634.

To a stirred solution of ester (10 mg, 20.8 μmol) in methanol (1.5 mL) was added K_2CO_3 (3 mg, 20.8 μmol) at O°C. The resulting mixture was stirred for 1.5 h at 0 °C. Ethyl acetate and water was then added and the usual workup gave a crude product, which was purified on silica gel using 20% EtOAc/CH_2Cl_2 to give the desired alcohol (+)-**52** (6.5 mg, 96%) as a colourless thin film.

*4.1.40. Diol (+)-**4**.* To a stirred solution of the ether (+)-**52** (12 mg, 36.1 μmol) in CH_2Cl_2 (2.4 mL) was added 9-iodo-9-BBN (100 μL, 100 μmol, 1 M in hexanes) at 0 °C. After stirring for 2 h at 0 °C, water was added and the stirring continued for a further 15 min. The reaction mixture was extracted with EtOAc and the usual workup gave a residue, which was purified on silica gel using 20% EtOAc/CH_2Cl_2 to afford the diol (+)-**4** (10 mg, 87%) as a pale yellow gum: $[\alpha]_{D^{17}}$ +5.6 (*c* 0.41, MeOH), lit.[10a] $[\alpha]_D$ +6.8 (*c* 0.16, MeOH), lit. (enantiomer)[11b] $[\alpha]_{D^{20}}$ −4.5 (*c* 0.15, MeOH); ^1H NMR (400 MHz, acetone-d_6) δ 1.48 (ddd, *J*=12.8, 8.4, 8.4 Hz, 1H, H12), 1.50 (ddd, *J*=12.8, 8.0, 4.8 Hz, 1H, H12), 1.57 (ddd, *J*=14.8, 2.4, 2.0 Hz, 1H, H14), 1.67 (ddd, *J*=12.8, 7.2, 6.8 Hz, 1H, H10), 1.83 (ddd, *J*=14.8, 10.8, 10.6 Hz, 1H, H14), 1.92 (ddd, *J*=12.8, 4.4, 4.4 Hz, 1H, H10), 2.29–2.41 (m, 2H, H1′), 2.43 (dd, *J*=14.8, 1.2 Hz, 1H, H8), 3.33 (dd, *J*=14.8, 9.6 Hz, 1H, H8), 3.79 (d, *J*=4.4 Hz, 1H, O*H*), 3.87 (m, 1H, H9), 3.98 (m, 1H, H11), 4.26 (m, 1H, H13), 5.03 (dddd, *J*=10.2, 2.0, 1.6, 1.6 Hz, 1H, H3′), 5.13 (dddd, *J*=17.2, 2.0, 1.6, 1.6 Hz, 1H, H3′), 5.47 (dddd, *J*=10.6, 5.6, 5.6, 2.4 Hz, 1H, H15), 5.91 (dddd, *J*=17.2, 10.2, 7.2, 6.8 Hz, 1H, H2′), 6.68 (d, *J*=7.6 Hz, 1H, H4), 6.76 (d, *J*=8.0 Hz, 1H, H6), 7.10 (dd, *J*=8.0, 7.6 Hz, 1H, H5), 8.39 (s, 1H, ArO*H*); ^{13}C NMR (100 MHz, acetone-d_6) δ 39.0, 39.7, 39.9, 40.1, 40.3, 64.8, 68.0, 73.6, 73.5, 114.3, 117.4, 122.3, 125.4, 130.2, 135.3, 140.2, 154.3, 169.2; HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ [M+Na^+]: 341.1365, found: 341.1364.

Acknowledgements

We thank the Australian Research Council for funding.

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